[Frontiers in Bioscience E4, 1582-1605, January 1, 2012]

Therapeutic targets of brain insulin resistance in sporadic Alzheimer's disease

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1. ABSTRACT

Growing evidence supports roles for brain insulin and insulin-like growth factor (IGF) resistance and metabolic dysfunction in the pathogenesis of Alzheimer's disease (AD). Whether the underlying problem stems from a primary disorder of central nervous system (CNS) neurons and glia, or secondary effects of systemic diseases such as obesity, Type 2 diabetes, or metabolic syndrome, the end-results include impaired glucose utilization, mitochondrial dysfunction, increased oxidative stress, neuroinflammation, and the propagation of cascades that result in the accumulation of neurotoxic misfolded, aggregated, and ubiquitinated fibrillar proteins. This article reviews the roles of impaired insulin and IGF signaling to AD-associated neuronal loss, synaptic disconnection, tau hyperphosphorylation, amyloid-beta accumulation, and impaired energy metabolism, and discusses therapeutic strategies and lifestyle approaches that could be used to prevent, delay the onset, or reduce the severity of AD. Finally, it is critical to recognize that AD is heterogeneous and has a clinical course that fully develops over a period of several decades. Therefore, early and multi-modal preventive and treatment approaches should be regarded as essential.

2. INTRODUCTION

The gold standard for definitively diagnosing AD is to perform a postmortem examination of the brain, with the objective of demonstrating beyond-normal aging associated densities of neurofibrillary tangles, neuritic plaques, and amyloid-ß 40-42 kD fragments of amyloid-ß precursor protein (AßPP-Aß) deposits in corticolimbic structures, bearing in mind that neurodegeneration frequently involves multiple other cortical regions as well. The common thread among these characteristic lesions is that they harbor insoluble aggregates of abnormally phosphorylated and ubiquitinated tau, and neurotoxic AßPP-Aß in the form of oligomers, fibrillar aggregates, or extracellular plaques. Secreted AßPP-Aß oligomers have been demonstrated to be neurotoxic and to inhibit hippocampal long-term potentiation, i.e. synaptic plasticitym (1).

To improve diagnosis and treatment, we must learn to connect the development and progression of neurodegeneration with molecular, biochemical, physiological, neuro-imaging, and clinical abnormalities in AD. Several strategies could be taken to advance this process. One is to consider the roles of other major abnormalities, including loss of neurons, fibers, and synapses, disruption of the cortical-laminar architecture, gliosis, proliferation of dystrophic neurites, and neuro-inflammatory responses. A second matter is to recognize and possibly embrace the significance of the considerable overlap among various subtypes of neurodegeneration with respect to their underlying cellular, molecular, biochemical, and structural abnormalities. The former approach could provide more options for discovering neurodegeneration and the latter could help define panels of biomarkers for diagnosing AD and distinguishing it from other forms of dementia. A third point is that the recognition of shared abnormalities among different neurodegenerative diseases may help to identify treatments and preventive measures that could be effective in all or most of them. Through the use of neuro-imaging, including positron emission tomography (PET) scanning, magnetic resonance imaging (MRI), functional MRI, and magnetic spectroscopy, combined with increasingly sophisticated molecular and biochemical analyses of postmortem brain tissue, it has become evident that neurodegenerative diseases share in common abnormalities in brain metabolism, accumulations of mis-folded ubiquitinated proteins (often cytoskeletal), oxidative stress, neuroinflammation, autophagy, and cell loss mediated by mitochondrial dysfunction, apoptosis, or necrosis. Therefore, attention must be paid to these multi-process mechanisms of neurodegeneration in considering therapeutic targets. Although this review focuses on AD, the concepts are very likely applicable to other major neurodegenerative diseases including fronto-temporal dementias, multiple systems atrophy, Parkinsonism-Lewy Body Dementia, and motor neuron diseases.

3. ALZHEIMER'S DISEASE: A BRAIN FORM OF DIABETES MELLITUS

Growing evidence supports the concept that Alzheimer's disease (AD) is fundamentally a metabolic syndrome in which brain glucose utilization and energy metabolism are impaired (2-6). These abnormalities have been linked to brain insulin and insulin-like growth factor (IGF) resistance with disablement of pathways needed for survival, gene expression, and plasticity in neurons (2). Inhibition of insulin/IGF signaling results in increased: 1) activity of kinases that cause tau to become hyper-phosphorylated; 2) accumulation of AßPP-Aß; 3) production of oxidative and endoplasmic reticulum (ER) stress; 4) oxidative damage to proteins, RNA, DNA, and lipids; 5) mitochondrial dysfunction; 6) neuro-inflammation; and 7) activation of pro-death cascades. The attendant down-regulation of target genes needed for cholinergic homeostasis, compromises learning, memory, and cognition.

Clues that AD actually represents a metabolic disease emerged from studies showing that deficits cerebral glucose utilization mark the early stages of disease (7-12), and that progression of metabolic abnormalities correlates with worsening of AD symptoms (13, 14). Recent studies showed that AD is associated with insulin and insulin-like growth factor (IGF) resistance and insulin/IGF deficiency in the brain, and are accompanied by significant and progressive abnormalities in the expression of genes and activation of kinases that are regulated by insulin and IGF (2-6). In fact, most if not all of the major abnormalities in AD, including deficits in choline acetyltransferase, hyper-phosphorylation of tau, increased oxidative stress, neuro-inflammation, activation of pro-AßPP-Aß cascades, and metabolic failure could be attributed to impaired insulin/IGF actions in the brain (5). Correspondingly, experimental down-regulation or depletion of brain insulin receptors is sufficient to cause cognitive impairment and neurodegeneration with features that overlap with AD (15-19). In AD brains, deficits in insulin/IGF signaling are due to the combined effects of insulin/IGF resistance and deficiency. Insulin/IGF resistance is manifested by reduced levels of insulin/IGF receptor binding and decreased responsiveness to insulin/IGF stimulation, while trophic factor deficiency is associated with reduced levels of insulin polypeptide and gene expression in brain and cerebrospinal fluid (CSF) (4-6, 20-22). In essence, AD can be regarded as a form of brain diabetes that has elements of both insulin resistance and insulin deficiency. To consolidate this concept, we proposed that AD be referred to as, "Type 3 diabetes" (5, 6).

4. SYSTEMIC DISEASE FACTORS CONTRIBUTING TO BRAIN INSULIN/IGF RESISTANCE AND AD NEURODEGENERATION

Aging is the most dominant risk factor for AD. This means that a host of intrinsic, environmental, and epigenetic factors that contribute to the process of aging establish the circumstances needed for neurodegenerative diseases to become manifested. The corollary is that the factors governing development of neurodegenerative diseases are not strictly genetic and therefore can be modified or prevented. Correspondingly, epidemiologic, clinical, and experimental data indicate that peripheral insulin resistance associated with obesity, Type 2 diabetes

mellitus (T2DM), metabolic syndrome (dyslipidemic states), and non-alcoholic steatohepatitis (NASH), can all mediate brain insulin/IGF resistance, and thereby contribute to the pathogenesis of mild cognitive impairment (MCI), dementia, or AD (3, 4, 22-29). More recently, human and experimental animal studies have provided new information about the causes and effects of brain insulin resistance and deficiency, particularly in relation to cognitive impairment (5, 6, 19, 30-33). The near globalization of the obesity epidemic is sounding alarms that now draw all of our attentions (23, 34). However, expansion of the literature often yields confusion from conflicting results and variability in study design. In order to develop logical and novel approaches for treating and preventing neurodegeneration based on the brain insulin resistance hypothesis, three main questions must be addressed: 1) Do T2DM and other peripheral insulin resistance states cause neurodegeneration, including AD? 2) Do T2DM and other peripheral insulin resistance disease states principally serve as co-factors in the pathogenesis of cognitive impairment and neurodegeneration? or 3) Do T2DM and AD fundamentally represent the same disease processes occurring in different target organs and tissues? These questions are addressed below.

4.1. Contributions of obesity and T2DM to cognitive impairment and neurodegeneration

Epidemiologic studies demonstrated that individuals with glucose intolerance, deficits in insulin secretion, or T2DM have a significantly increased risk of developing mild cognitive impairment (MCI) or AD-type dementia. Longitudinal studies further suggested that T2DM (35, 36) and obesity/dyslipidemic disorders (37) correlated with eventual development of MCI, dementia, or AD (35, 38-43). However, one study showed that obesity itself, with or without superimposed T2DM, increased the risk for MCI, AD, or other forms of neurodegeneration (44), suggesting that systemic factors related to obesity, besides T2DM, can promote neurodegeneration. On the other hand, although a relatively high percentage of individuals with MCI or dementia have T2DM, peripheral insulin resistance, or obesity, the vast majority of patients with AD do not have these diseases. To gain a better understanding of the contributions of T2DM and obesity to neurodegeneration, attention must be given to postmortem human and experimental animal studies.

In general, the arguments made in favor of the concept that T2DM or obesity causes AD are not founded; however, the concept that peripheral insulin resistance disease states contribute to cognitive impairment and AD pathogenesis or progression does have a sound basis. Against a causal role are the findings that, postmortem human brain studies demonstrated no significant increase in AD diagnosis among diabetics (45), and similarly abundant densities of senile plaques and rates of neurofibrillary tangle pathology were observed in subjects with T2DM compared with normal aged controls, although peripheral insulin resistance was more common in AD than with normal aging (46). Since neurofibrillary tangles and dystrophic neurites are hallmarks of AD and correlate with severity of dementia, the abovementioned findings in human postmortem studies indicate that T2DM alone is not sufficient to cause AD. On the other hand, in experimental mouse and rat models, chronic high fat diet (HFD) feeding and diet induced obesity (DIO) with associated T2DM, do cause cognitive impairment with deficits in spatial learning and memory (47, 48). Moreover, experimental obesity with T2DM causes mild brain atrophy with brain insulin resistance, neuro-inflammation, oxidative stress, and deficits in cholinergic function (49, 50).

An important qualifier concerning these studies is that the associated brain abnormalities in diabetes and obesity syndromes were typically modest in severity, and devoid of many important structural lesions that characterize AD, i.e. neurofibrillary tangles. Therefore, observations in both in humans and experimental models suggest that while obesity or T2DM can be associated with cognitive impairment, mild brain atrophy, and a number of AD-type biochemical and molecular abnormalities in brain, including insulin resistance and oxidative stress, they do not cause significant AD pathology. Instead, the findings suggest that T2DM, obesity, and probably other peripheral/systemic insulin resistance states serve as co-factors contributing to the pathogenesis or progression of neurodegeneration. The significance of these results is that therapeutic strategies designed to treat T2DM, obesity, and systemic insulin resistance could help slow the progress or reduce the severity of AD, but they will not likely prevent it altogether. Correspondingly, a number of studies have already demonstrated that treatment with hypoglycemic or insulin sensitizer agents can be protective in reducing the incidence and severity of AD brain pathology (51).

4.2. Pathological processes contributing to cognitive impairment and neurodegeneration in states of systemic insulin resistance

T2DM, obesity, and peripheral insulin resistance may contribute to MCI, dementia, and neurodegeneration as a result of chronic hyperglycemia, peripheral insulin resistance, oxidative stress, advanced glycation end-products accumulation, insulin degrading enzyme activation, inflammation, and/or microvascular disease (42). Chronic hyperglycemia, peripheral insulin resistance, oxidative stress, and advanced glycation end-product accumulation can cause progressive injury to vessel walls and eventual fibrosis. Insulin degrading enzyme has a role in the processing AßPP, and in states of insulin deficiency or resistance, insulin degrading enzyme may be rendered more available for AßPP cleavage and attendant AßPP-Aß deposition in vessel walls. Finally, the contribution of dyslipedemic states associated with T2DM, obesity, and hepatic steatosis is such that toxic lipids, particularly ceramides, can cause insulin resistance. Their increased levels in peripheral blood in peripheral insulin resistance disease states may contribute to progressive insulin resistance in cerebral vessels and brain parenchyma, accounting for the excessive overlap of AD with cerebral micro-vascular disease.

4.2.1. Vascular factors

The role of cerebral microvascular disease deserves particular attention because of its long recognized

association with AD. Cerebrovascular disease can additively impact the development and progression of dementia by causing multifocal ischemic lesions, focal infarcts in structures targeted by AD, or leukoaraiosis with pronounced attrition of white matter fibers (52). Diabetes mellitus causes arteriosclerosis, in part due to chronic hyperinsulinemia, which injures blood vessels, causing intimal thickening, scarring, and leakiness (53-58). In addition, hyperinsulinemic diabetics who also carried at least one ApoE-ε4 allele were found to have a compounded risk for developing AD, whereas non-diabetic, ApoE4-ε4 negative individuals showed significantly lower densities of AßPP-Aß plaques and neurofibrillary tangles by postmortem examination.

4.2.2. Neurotoxic lipids

Recent studies suggest that cognitive impairment correlates more with hepatic steatosis and insulin resistance than obesity or T2DM (59-65). Correspondingly, neurocognitive deficits and brain insulin resistance occurred primarily when chronic high calorie feeding resulted in visceral obesity with steatohepatitis. Moreover, a number of examples showed that high fat intake and obesity were not required, and instead, toxin exposures that caused steatohepatitis with hepatic insulin resistance also resulted in neurodegeneration and cognitive impairment (19, 33, 49, 50, 66, 67). These observations suggest that hepatic insulin resistance may mediate neurodegeneration.

Hepatic insulin resistance dysregulates lipid metabolism, resulting in increased oxidative and ER stress, mitochondrial dysfunction, and lipid peroxidation (68, 69). Sustained hepatic insulin resistance leads to increased lipolysis (70) and the generation of toxic lipid e.g. ceramides, which further impair insulin signaling, mitochondrial function, and cell viability (69, 71, 72). Ceramides are lipid signaling molecules (73) that cause insulin resistance (74-76) by activating pro-inflammatory cytokines (73, 77, 78) and impairing PI3 kinase-Akt activation (79-82). Hepatic ceramide production increases in various models of steatohepatitis, including diet-induced obesity (DIO) and low-level nitrosamine exposure (19, 33, 49, 66, 67), and each is associated with cognitive impairment, brain insulin resistance, and neurodegeneration. This point led us to formulate the hypothesis that, in the settings of obesity, T2DM, and other peripheral insulin resistance states, cognitive impairment is mediated via a liver-brain axis of neurodegeneration (83-85).

4.2.3. Liver brain axis hypothesis

In essence, cognitive impairment with neurodegeneration and brain insulin resistance is caused by the increased generation of ceramides in liver, which enter peripheral blood, and cross the blood-brain barrier to produce neuronal insulin resistance, oxidative stress, and molecular and biochemical abnormalities that lead to AD (86). This hypothesis is supported by experiments showing that parenteral administration of cytotoxic ceramides produces sustained impairments in spatial learning and memory with neurodegeneration and brain insulin/IGF resistance, similar to the effects of DIO with T2DM and NASH Preliminary studies showed that chemical inhibitors of ceramide biosynthesis enhance insulin sensitivity, and treatment with peroxisome proliferator-activated receptor (PPAR) agonists, e.g. PPAR-α (GW7647), PPAR-δ (L-160,043), or PPAR-γ (F-L-Leu), which improve insulin responsiveness and reduce oxidative stress (33, 87-89), decrease hepatic ceramide generation, serum ceramide levels, cognitive impairment, and neurodegeneration in models of DIO with T2DM and steatohepatitis (90). Therefore, we propose that peripheral insulin resistance diseases contribute to neurodegeneration, including AD, by increasing production of neurotoxic ceramides that cause brain insulin resistance.

5. CENTRAL NERVOUS SYSTEM PATHOGENIC FACTORS MEDIATING PRIMARY BRAIN INSULIN/IGF RESISTANCE (TYPE 3 DIABETES)

A compelling argument has been made that AD represents a brain form of diabetes mellitus (5, 6). AD is associated with progressive brain insulin resistance in the absence of T2DM, obesity, or peripheral insulin resistance (5, 6, 31, 32), and the molecular, biochemical, and signal transduction abnormalities in AD are virtually identical to those that occur in both T1DM and T2DM (5, 6, 35, 91-95). This hypothesis is supported by experimental studies in which, the administration of intracerebroventricular streptozotocin, a glucosamine-nitrosourea pro-diabetes compound, resulted in cognitive impairment with deficits in spatial learning and memory, brain insulin resistance and insulin deficiency, and AD-type neurodegeneration, but not diabetes mellitus (19, 96-99). In contrast, parenteral administration of streptozotocin causes diabetes mellitus with relatively mild degrees of hepatic steatosis and neurodegeneration (96, 100-102). The alkylating properties of streptozotocin cause DNA damage, and uptake of streptozotocin by insulin producing cells, i.e. pancreatic islet ß cells, leads to insulin deficiency and hyperglycemia (Type 1 diabetes). However, the broader effects of low or high dose streptozotocin treatments suggest that the glucosamine-nitrosourea actions extend well beyond inducing toxic injury to insulin producing cells. These observations suggest that diabetes mellitus syndromes with impairments in insulin signaling and energy metabolism, and increased oxidative stress, mitochondrial dysfunction, and cell death, can selectively target one or more organ-systems including liver, skeletal muscle, adipose tissue, kidney, or brain. This concept is not unique since vascular, autoimmune, and malignant neoplastic diseases can also selectively or differentially afflict different organ systems. But, what pathological or physiological factors are responsible for the selective occurrence of insulin/IGF resistance in the brain?

5.1. Role of tau pathology in the pathogenesis of type 3 diabetes

Neurofibrillary tangles and dystrophic neuritis represent the major neuronal cytoskeletal lesions that correlate with dementia in AD. These structural abnormalities contain aggregated and ubiquitinated insoluble fibrillar microtubule-associated proteins, particularly tau. (103, 104). Tau protein gets hyper-

phosphorylated due to inappropriate activation of kinases, such as GSK-3ß. Consequently, tau protein misfolds and self-aggregates into insoluble fibrillar structures that form neurofibrillary tangles, dystrophic neurites, and neuropil threads (105). Accumulation of fibrillar tau disrupts neuronal cytoskeletal networks and axonal transport, leading to synaptic disconnection and neurodegeneration (105). In addition, pre-fibrillar tau can aggregate into soluble neurotoxic oligomers that cause synaptic disconnection and neuronal death (106).

Although the key steps leading to tau hyper-phosphorylation and aggregation could be explained on the basis of brain insulin/IGF resistance (107-110), due to the associated decreased signaling through phosphoinositol-3-kinase (PI3K), Akt (28, 29), and Wnt/β-catenin (111), and increased activation of GSK-3β (112-116), tau hyper-phosphorylation mediated by other mechanisms such as increased activation of cyclin-dependent kinase 5 (cdk-5) and c-Abl kinases (117, 118), and inhibition of protein phosphatases 1 and 2A (105, 118, 119), could lead to oxidative stress and neuro-inflammation, which are inhibitory to insulin/IGF signaling.

5.2. Contributions of Amyloid-β neurotoxicity in type 3 diabetes

In AD, amyloid precursor protein (AßPP) expression and processing are dysregulated, resulting in the accumulation of AßPP-Aß (Aß) soluble neurotoxic oligomeric fibrils, and insoluble aggregated fibrils (plaques). Increased AßPP expression and altered proteolysis result in formation and accumulation of 40 or 42 amino acid length Aß peptides that can aggregate. The causes of Aß accumulation and toxicity in sporadic AD are still unknown. However, experimental evidence supports opposing arguments that brain insulin resistance with attendant oxidative stress and neuro-inflammation promotes Aß accumulation and toxicity, and that Aß toxicity causes brain insulin resistance.

Insulin stimulation accelerates trafficking of Aβ from the trans-Golgi network, where it is generated, to the plasma membrane, and insulin stimulates Aß extracellular secretion (120) and inhibits its intracellular accumulation and degradation by insulin-degrading enzyme (121, 122). Therefore, impaired insulin signaling can disrupt both the processing of AßPP and clearance of Aß (123). On the other hand, accumulation of Aβ disrupts insulin signaling by competing with insulin, or reducing the affinity of insulin for binding to its own receptor (124, 125). In addition, AßPP oligomers inhibit neuronal transmission of insulin-stimulated signals by desensitizing and reducing the surface expression of insulin receptors, and intracellular AßPP-Aß directly interferes with PI3 kinase activation of Akt, which leads to impaired survival signaling, increased activation of GSK-3ß, and hyper-phosphorylation of tau. Since IGF-1 or IGF-2 suppression of GSK-3ß activity (126) reduces the neurotoxic effects of AßPP (127-130), the neuro-protective properties of these and related trophic factors could be exploited for therapeutic purposes in AD.

5.3. Stress factors in the pathogenesis of brain insulin resistance

Insulin and IGF signaling regulate glucose utilization, metabolism, and ATP synthesis needed for cellular homeostasis and broad ranging functions. Deficits in cerebral glucose utilization and energy metabolism occur early in AD, either prior to, or coincident with initial stages of cognitive decline (22, 131, 132). Correspondingly, impairments in brain insulin and IGF signaling mechanisms correlate with severity of AD (6). Since glucose transporter 4 (GLUT4) regulates brain glucose uptake and utilization, and GLUT4 expression and function are stimulated by insulin, brain insulin resistance could readily account for the deficits in energy metabolism that begin early in the course of AD. Deficits in energy metabolism lead to increased oxidative stress, mitochondrial dysfunction, and pro-inflammatory cytokine activation (16, 109, 133). Oxidative stress promotes the accumulation of reactive oxygen (ROS) and reactive nitrogen species (RNS) that attack subcellular organelles, resulting in adducts with DNA, RNA, lipids, and proteins, and attendant compromise of their structural and functional integrity. Consequences include, loss of cell membrane functions, disruption of the neuronal cytoskeleton with attendant synaptic disconnection, neurotransmitter deficits, and impaired neuronal plasticity, and neuro-inflammation. Neuro-inflammatory responses in microglia and astrocytes increase oxidative stress, organelle dysfunction, and pro-apoptosis signaling. However, neuro-inflammation can also contribute to brain insulin/IGF resistance because it stimulates AßPP expression (134), and aberrant AßPP cleavage, deposition, and toxic fibril formation in the brain (130, 135-139). In addition, persistent oxidative stress and neuro-inflammation lead to constitutive activation of kinases e.g. GSK-3ß, which promote aberrant hyper-phosphorylation of tau. Therefore, although brain insulin/IGF resistance causes oxidative stress, neuro-inflammation, and energy dyshomeostasis, oxidative stress can also precipitate or exacerbate brain insulin/IGF resistance and thereby worsen neurodegeneration (5, 26, 33).

5.4. Reverberating loop of neurodegeneration

In sporadic AD in which brain diabetes is the main or only manifestation of insulin/IGF resistance in the body, the initiating and etiological factors are not known. However, experimental data cited above, support seemingly opposing arguments that hyper-phosphorylated tau, aberrant amyloid-ß processing, oxidative stress, and neuro-inflammation both cause and can be caused by brain insulin/IGF resistance. The significance of the aggregate results is that, once the cascade of neurodegeneration has been established, it can be exacerbated and perpetuated by the very pathological processes that are caused by the initiating factors. Therefore, the process of neurodegeneration can cyclically spiral toward more advanced stages of disease, and ultimately result in permanent changes that are no longer amenable to treatment.

6. ENVIRONMENTAL/EXPOSURE FACTORS POTENTIALLY MEDIATING BRAIN INSULIN/IGF RESISTANCE AND NEURODEGENERATION

The argument that aberrant phosphorylation of tau, AßPP protein processing, and neuroinflammation are causal, i.e. major initiating factors in the pathogenesis of brain insulin/IGF resistance is weakened by the fact that these pathological processes have no known primary causes, and a large number of studies have thoroughly documented that intracerebral treatment with streptozotocin, a pro-diabetes drug, not only causes brain insulin/IGF resistance, but also leads to increased tau phosphorylation, AßPP accumulation, and neuro-inflammation (15, 18, 19, 33, 140). In addition, intracerebral delivery of short interfering RNA (si-RNA) duplexes to inhibit insulin, IGF-1, or IGF-2 receptor expression and signaling in the brain or cultured neurons was found to be sufficient to increase tau phosphorylation, AßPP-Aß expression, oxidative stress, mitochondrial dysfunction, and neuronal death (141). Together, the intracerebral streptozotocin and si-RNA studies support a primary role for brain insulin/IGF resistance (brain diabetes) as the initiating factor in the pathogenesis of AD and its protein molecular and biochemical lesions. However, the missing link is what could possibly cause brain (type 3) diabetes? The answer is most likely connected to the same factors responsible for our epidemics of Type 2 diabetes, non-alcoholic steatohepatitis, and metabolic syndrome.

6.1. Environmental toxins/exposures as mediators of type 3 diabetes

Despite overwhelmingly convincing data that AD represents a brain form of diabetes, conclusions drawn from the intracerebral streptozotocin experiments raise questions because streptozotocin is generally not available to humans. Over the past several years, our group has wrestled with this puzzle. The startling realization that streptozotocin is actually a nitrosamine-related compound that is routinely used to generate models of Type 1 and Type 2 diabetes, prompted us to probe potential links between nitrosamine exposures and diabetes mellitus or AD. Over the past several decades, Western societies have endured continuous and growing exposures to environmental and food-related nitrosamines. The curves corresponding to exposure rates through processed foods precede and parallel those for AD and diabetes mortality, irrespective of age group (34). Since nitrosamines are mutagenic and cause cancers in many organs, we posed the question as to whether low and limited exposures to nitrosamines could cause insulin resistance instead of cancer.

We conducted experiments using brief exposures to sub-mutagenic doses of nitrosamine compounds that are commonly found in processed and preserved foods, e.g. N-nitrosodiethylamine (NDEA), and determined the long-term effects on insulin/IGF signaling networks in the body, liver, and brain. Those studies revealed that low-dose NDEA exposures cause T2DM, non-alcoholic steatohepatitis, visceral obesity, cognitive impairment, and AD-type neurodegeneration with peripheral, hepatic, and brain insulin resistance (66, 67), similar to the effects of streptozotocin. Moreover, the adverse effects of NDEA on neuro-cognitive deficits, peripheral, hepatic, and brain insulin resistance, steatohepatitis, and neurodegeneration were exacerbated by chronic high fat diet feeding (142, 143). Therefore, depending on the structure of the compound, dose, and route of administration, nitrosamines and related chemicals can cause insulin resistance diseases in multiple different target organs, including brain. These results provide evidence that the relatively recent epidemics of sporadic AD, T2DM, and non-alcoholic steatohepatitis/metabolic syndrome could be mediated by environmental or dietary exposures (34), and show that insulin resistance diseases with essentially the same underlying cellular abnormalities, can develop in various organs and tissues. Moreover, these findings correspond with the overlapping increases in prevalence of various insulin resistance diseases, and the very frequent co-occurrences of AD with obesity, T2DM, of NASH (46), which did not exist prior to 1980, and is not accounted for by aging of the population (34). It is noteworthy that nearly two decades ago, mutagenic nitroso compounds were recognized to also cause insulin resistance diseases (144-146).

7. POTENTIAL THERAPEUTIC TARGETS FOR AD

The metabolic/brain insulin resistance hypothesis can account for nearly all abnormalities that characterize the AD neurodegeneration cascade, including progressively increased oxidative stress and ROS generation, mitochondrial dysfunction, cell death, loss of synaptic plasticity, deficits in cholinergic homeostasis, increase expression of AßPP, hyper-phosphorylation of tau, compromised myelin maintenance, and neuro-inflammation. Correspondingly, it is important to bear in mind that AD fundamentally represents a metabolic disease associated with the same molecular, biochemical, and cell signaling abnormalities identified in peripheral insulin resistance diseases. Therefore, it may be possible to treat or prevent progression of AD based on stage and severity of brain insulin resistance, similar to approaches used to treat T2DM, obesity, non-alcoholic steatohepatitis, and metabolic syndrome. At the same time, it is important to recognize that AD is the end result of a neurodegeneration cascade that targets and progressively cripples different aspects of cellular physiology and homeostasis. Therefore, it should anticipated that while mono-therapies may be appropriate, and instead, multi-pronged approaches will likely be needed to support a range of nervous system functions and minimize cellular injury and toxicity as the disease progresses.

7.1. Targeting insulin deficiency

AD is associated with brain insulin deficiency (reduced brain and CSF levels), with or without associated systemic insulin resistance or T2DM. Proposed therapeutic strategies designed to rectify brain insulin deficiency in AD, are supported by the findings that: 1) diabetic patients that are well-managed with insulin exhibit significant improvements in memory and slowing of AD progression;

Table 1. Therapeutic targeting of brain insulin resistance in Alzheimer's disease

Target	Agent	Mechanism of Action
Aβ42 accumulation and fibrillarization	Gamma secretase inhibitor drugs (Notch sparing); BACE1 inhibitors to reduce cleavage and production of toxic peptides	Reduces insulin resistance, enhances PI3K-Akt signaling; reduces GSK-3ß activity resulting in decreased tau phosphorylation
Tau hyperphosphorylation	GSK-3ß inhibitors and protein phosphatase 2A agonists	Reduces oxidative stress, helps restore insulin responsiveness
Insulin deficiency	Insulin therapy-intranasal Incretins, e.g. GLP-1 to stimulate insulin	Maintains survival and function of cells requiring insulin stimulation; supports glucose uptake, brain metabolism and neuronal plasticity; Decreases AßPP burden and tau hyperphosphorylation; Enhances cognition
Hyperglycemia	Antihyperglycemic agents-biguanides	Enhance glucose uptake and insulin receptor sensitivity
Insulin resistance	Insulin sensitizers, e.g. PPAR agonists	Enhance glucose uptake and insulin receptor sensitivity; anti-inflammatory and anti-oxidant properties
Oxidative stress and Neuro-inflammation	Anti-oxidants Radical scavengers Anti-inflammatory agents Transition metal chelators	Help restore insulin sensitivity and glucose utilization Reduce Aβ42 deposition Reduce Aβ42 and tau fibrillarization Reduce cytokine activation-mediated injury Supports microvascular function and cerebral perfusion

Abbreviations: BACE1=ß site AßPP cleaving enzyme 1; GLP-1=glucagon-like peptide-1; PPAR= peroxisome proliferator-activated receptor; PI3K= phosphoinositol-3- kinase; GSK-3ß = glycogen synthase kinase 3ß; AßPP= amyloid-ß - precursor protein; Aß 42=amyloid-ß peptide-42 amino acids 1-42 cleavage product; IGF=insulin-like growth factor

2) elderly diabetics that were treated with insulin had lower densities of AD lesions compared with non-diabetic controls; 3) insulin administration improves cognition and memory in AD, and insulin stimulated cognition is correlated with increased levels of norepinephrine in both plasma and CSF (147); 4) hyper-insulinemic euglycemic clamping enhances cognition and attention in patients with AD; and 5) experimental intracerebral or intravenous treatments with insulin improve memory, cognition, evoked brain potentials, and neurotransmitter function (123). Although attractive and seemingly simple, a foremost consideration is that the subject population consists of elderly individuals who would be at increased risk for developing complications from inadvertent bouts of hypoglycemia, e.g. traumatic falls, that could be debilitating or life-threatening, and metabolic insults to various organs, including brain. Moreover, the effectiveness of insulin therapy may be dependent upon simultaneously increased levels/availability of glucose, and may not improve memory if CSF AßPP-Aß42 levels are markedly elevated due to insulin resistance (148). Therefore, systemic insulin therapy for patients with AD is not feasible.

7.1.1. Intranasal insulin therapy

Intranasal insulin can be administered to AD subjects because it does not produce the harmful side-effects of systemic insulin treatment (Table 1). Intranasal insulin increases brain insulin levels and improves performance on declarative memory tasks while having little effect on plasma glucose and insulin levels (149). In addition, intranasal insulin delivered via an electronic atomizer, improves attention and increases the AßPP-Aß 40/AßPP-Aß42 ratio (150). Reducing the relative amounts of AßPP-Aß42 should be neuroprotective as AßPP-Aß42 is the neurotoxic form of the secreted peptide. In a controlled clinical trial, ApoE-ε4-negative individuals were found to benefit significantly from intranasal insulin, as manifested by improvements in cognitive performance (149). The fact that ApoE-ε4+ subjects failed to benefit from the same treatment suggests that intranasal insulin, as well as other pro-metabolic therapies for AD, may have to be tailored according to particular genetic risk factors and biomarkers of disease.

7.1.2. Insulin stimulating/releasing hormones (incretins)

As an alternative to insulin, incretins, such as glucagon-like peptide-1 (GLP-1), may help restore insulin levels in the brain. GLP-1 is an insulinotropic peptide that is generated by cleavage of proglucagon protein. GLP-1 is rapidly degraded by dipeptidyl peptidase-4, and therefore is quite safe. GLP-1 stimulates insulin gene expression and secretion, and suppresses glucagon. GLP-1 lowers blood glucose in individuals with T2DM (151, 152), and it restores insulin sensitivity. The dual actions of incretins in stimulating insulin secretion and enhancing insulin responsiveness make GLP-1 and related molecules very attractive for treating AD. Like insulin, GLP-1 stimulates neuritic growth in CNS neurons and exerts neuroprotecive actions against glutamate-mediated excitotoxity, oxidative stress, trophic factor withdrawal, and cell death (153-155). In addition, inhibition of dipeptidyl peptidase-4, which degrades GLP-1, reduced oxidative and nitrosative stress, inflammation, memory impairment, and AßPP-Aß deposits in an AD transgenic mouse model (156). Importantly, GLP-1 can cross the blood-brain barrier, and may effectively reduce brain AßPP-Aß burden in AD (151, 152, 157). With the realization that GLP-1 has a short half-life and therefore limited practical use for long-term therapy, synthetic long-lasting analogues of GLP-1 have proven to be effective in preserving cholinergic neuron function (158). The development of GLP-1 receptor agonists, such as Geniposide or Extendin-4, which harbor the same neuro-protective and neuro-stimulatory properties as GLP-1 (159), but have longer half-lives (153, 157, 160, 161), may provide effective and standardized long-term options for treating brain insulin resistance diseases such as AD. Finally, a future approach could be to genetically modify mesenchymal or stem cells to provide sustained delivery of neuro-stimulatory and neuro-protective agonists (162-164), including GLP-1 (165).

7.2. Targeting insulin resistance

Human clinical and postmortem studies have documented that AD is associated with brain insulin

resistance, with or without associated systemic insulin resistance or T2DM.

7.2.1. Anti-hyperglycemic agents

Metformin is a biguanide anti-hyperglycemic drug that is used to treat T2DM. Metformin suppresses gluconeogenesis and enhances glucose uptake and insulin sensitivity. Metformin protects against neurological complications of T2DM, including cognitive impairment and cerebral vascular disease (166). Although metformin treatment was found to increase the generation of both intra- and extracellular AßPP-Aß due to increased expression of ß-secretase 1 (BACE1), administration of insulin plus metformin paradoxically provides significant neuroprotection, reduces AßPP-Aß levels, and decreases the severity of AD pathology, including AßPP-Aß neuritic plaques, and oligomeric AßPP-Aß-mediated down-regulation of the insulin receptor. Therefore, while metformin mono-therapy may be harmful due to its exacerbation of AD-type neurodegeneration (167), when combined with insulin, it may benefit elderly patients in the early stages of AD, by significantly improving cognitive performance and slowing the rate of neurodegeneration.

7.2.2. Insulin sensitizers

Peroxisome proliferator-activated receptor (PPAR) agonists are steroid hormone super family ligand-inducible transcription factors that enhance insulin sensitivity, modulate glucose and lipid metabolism, stimulate mitochondrial function, and reduce inflammatory responses (168-171). Three classes of PPARs are recognized, PPAR-α, PPAR-δ, and PPAR- γ. All 3 are expressed in the adult brain, although PPAR-δ is most abundant, followed by PPAR-γ (6, 33, 88). PPAR agonist treatments improve cognitive performance in experimental animal models (33, 172) and in humans with AD or MCI (87, 89, 173). The PPAR-γ agonist, rosiglitazone, has been most widely studied in human clinical trials. In addition to its insulin sensitizing and anti-inflammatory properties, rosiglitazone, like metformin, increases expression of the GLUT4 glucose transporter and glucose metabolism. Moreover, PPAR agonists such as, rosiglitazone, can enhance the therapeutic effects of metformin+insulin.

In a small double-blind, placebo-controlled trial, rosiglitazone treatment significantly preserved performance on delayed recall and attention tasks relative to the placebo-treated group, which continued to decline (174), but a later study found that rosiglitazone therapy mainly helped preserve cognition in patients who were ApoE-ε4-negative (175). More recently, the outcome of a rosiglitazone monotherapy, randomized double-blind placebo controlled phase III study was negative with respect to improvements in objective cognitive assessments, but highly statistically significant based on clinical and caregiver impression (176). Potential explanations for these disappointing results include the following: 1) effective treatment of neurodegenerative diseases may require a different isoform of PPAR agonist, i.e. PPAR-δ, since PPAR-δ is abundantly expressed in the brain, and previous studies showed that PPAR-δ agonist treatment more effectively prevented AD-type neurodegeneration and neurocognitive deficits compared with PPAR-α and PPAR-γ agonists (33); 2) the biodistribution of the PPAR agonists may not have been optimized based on the structure of the compounds; and 3) mono-therapy may not be sufficient, and instead the combined administration of a PPAR agonist with insulin or GLP-1 and metformin may be required to effectively treat AD-associated brain insulin resistance and metabolic dysfunction.

Insulin resistance states lead to metabolic imbalances with disturbances in carbohydrate and lipid metabolism. Perturbations in lipid metabolism result in states of lipotoxicity, which further increase insulin resistance. PPARs, including PPAR-γ, regulate energy balance by promoting dissipation or deposition of energy. PPAR-γ-coactivator 1α (PGC1-α) induces gene expression that promotes differentiation, and increases fatty acid oxidation via expansion of mitochondrial capacity and function (177). PGC1α binds to nuclear PPAR-γ, which then enables its interactions with various transcription factors that regulate mitochondrial biogenesis. In essence, PGC1-α is an important negative regulator of oxidative stress, mitochondrial dysfunction, lipotoxicity, and insulin resistance (177-179). The relevance of these data to AD is that genetic deficiencies in PGC1 α increase proneness to neurodegeneration (179, 180). This suggests that PGC1-α may represent an excellent therapeutic target for AD, and possibly other major neurodegenerative diseases as well.

7.3. Targeting tau pathology

Hyper-phosphorylation of tau promotes misfolding and aggregation of oligomeric fibrils. Subsequent protein ubiquitination results in the formation of insoluble, fibrillar aggregates and paired helical filaments, which comprise the cores of neurofibrillary tangles, neuropil threads, and dystrophic neurites, i.e. the structural hallmarks of AD neuropathology. Tau hyperphosphorylation is mediated by inappropriate and sustained activation of kinases, including glycogen synthase kinase-3ß (GSK-3ß) (181), cyclin-dependent kinase -5 (Cdk-5), p38 MAPK, and c-jun kinase (JNK) (182, 183), and inhibition of phosphatases that dephosphorylate tau, e.g. protein phosphatase-2A (183). Insulin resistance leads to increased activation of GSK-3ß as well as other kinases due to combined effects of inhibiting PI3K-Akt and increased oxidative stress. The increased oxidative stress induced by the accumulation of misfolded, aggregated cytoskeletal proteins exacerbates insulin resistance and neuroinflammation. Therefore, treatment with chemical inhibitors of one or more AD-relevant kinases may reduce the rates of neurofibrillary pathology and help prevent progressive brain insulin resistance.

Several studies focused on the role of GSK-3ß because, in addition to promoting tau hyper-phosphorylation, high levels of GSK-3ß activity lead to alterations in AßPP processing and increased neuronal death (181, 184-186). Approaches to therapeutically inhibit GSK-3ß activity have mainly included the use of lithium chloride, and to a lesser extent, indigoids (181, 184-187). In several uncontrolled or retrospective human studies, it was

found that prior use of lithium therapy protected against dementia and was associated with better performance on cognitive tests (188-191). In addition, chronic lithium treatment reduced the prevalence rates of AD and the brain activity levels of GSK-3ß, and it increased the levels of brain-derived neurotrophic factor in subjects at risk for early onset familial AD, (192). However, a subsequent randomized, single-blind, short-term (10 weeks) placebo-controlled multicenter trial proved disappointing in that performance on standardized cognitive function tests was not significantly improved, and no significant reductions in CSF GSK-3ß activity were detected (193). On the other hand, those data should to be interpreted with caution because of the short duration of the trial compared with earlier retrospective studies.

7.4. Reducing amyloid burden to restore insulin responsiveness

Research in the field of AD has extensively focused on finding safe and effective means of depleting the brain of toxic AßPP-Aß deposits, reducing the formation of toxic AßPP-Aß-derived diffusible ligands (ADDL) and oligomers, preventing AßPP-Aß fibrillarization and aggregation, increasing brain clearance of AßPP-Aß peptides, and decreasing abnormal cleavage of AßPP (194). The central hypothesis is that AßPP-Aß peptides are neurotoxic, promote amyloid plaque formation, and mediate tau hyper-phosphorylation, fibrillarization, and neurofibrillary tangle formation (195). Efforts to deplete the brain of toxic AßPP-Aß led to the development of AßPP-Aß-targeted immunotherapy. Although AßPP-Aß active immunization with AßPP-Aß peptides, or passive delivery of AßPP-Aß-specific antibodies can effectively clear AßPP-Aß plaques from human and experimental animal brains (196), the end results proved not very encouraging because the AßPP-Aß instead accumulated in vessels, increasing propensity for micro-hemorrhage (197). Moreover, the human subjects continued to decline and died with end-stage AD (198, 199). The treatments are not free of side effects because subjects can develop vasogenic cerebral edema (196, 199), i.e. pro-inflammatory responses with increased microglial activation, cerebral amyloid angiopathy, and accumulation of soluble neurotoxic oligomeric AßPP-Aß (200). Furthermore, although the administration of passive humanized AßPP-Aß antibody can clear AßPP-Abß from the brain (201), it has been difficult to demonstrate clinically significant improvements in progression from mild or moderate to severe dementia (202).

An approach to prevent the build-up of toxic AßPP-Aß and formation of ADDLs is to inhibit the expression or activity of enzymes that aberrantly process and cleave AßPP. AßPP-Aß is generated by sequential proteolysis by ß secretases, then γ-secretases (203). Presenilins (PS), which are often mutated in early onset familial AD, form the catalytic component of γ-secretases, which mediate intramembranous cleavage of type 1 transmembrane proteins, including AßPP (204). Mutation of PS genes leads to premature and excessive brain accumulations of AßPP-Aß (204). To inhibit abnormal processing of AßPP and accumulation of toxic AßPP-Aß, γ secretases have been targeted (205, 206). Although this approach seems promising for lowering plasma, CSF, and brain AßPP-Aß burden (203, 207), the objective clinical therapeutic responses have been minimal or undetectable (205, 208, 209). Worse yet, these drugs are highly toxic due to concurrent inhibition of Notch signaling (203, 206), which mediates neuronal plasticity, cognition, and long-term memory (210). To circumvent toxicity problems, efforts are underway to develop Notch cleavage-sparing γ secretase inhibitors (211, 212), but clinical trial results are not yet known.

Insulin accelerates trafficking of AßPP-Aß from the trans-Golgi network to the plasma membrane, and extracellular secretion of Aß (120), and impaired insulin signaling disrupts the processing of AßPP and clearance of AßPP-Aß (123). Therefore, by addressing the underlying causes of insulin/IGF resistance, we may be able to effectively and safely reduce AßPP-Aß burden in the brain. This point is reinforced by the finding that IGF-1 and IGF-2 are neuroprotective as they reduce the neurotoxic effects of AßPP (127-130). On the other hand, AßPP oligomers and ADDLs inhibit neuronal insulin-stimulated signals, blocking PI3 kinase activation of Akt, which leads to impaired survival signaling, increased activation of GSK-3ß, and resultant hyper-phosphorylation of tau. This suggests that efforts to reduce AßPP oligomer fibrillarization as a means of restoring brain insulin sensitivity should continue to be pursued.

7.5. Antioxidant and anti-inflammatory drugs

Antioxidants help maintain mitochondrial homeostasis, neuronal activities, and cell survival. Oxidative stress plays a pivotal role in the pathogenesis and progression of AD. Sources of oxidative stress include, impaired insulin signaling, fibrillarization of oligomeric AßPP-Aß and tau, mitochondrial dysfunction, micro-vascular disease, accumulation of reactive oxygen species (ROS) and reactive nitrogen species (RNS), and inflammation (213). Although it has not yet been determined which source of oxidative stress in most critical to neurodegeneration and cognitive impairment, some doubt has been cast upon the role of AßPP-Aß since in a longitudinal analysis, significant reductions in plasma AßPP-Aß42 in subjects treated with various anti-inflammatory agents, was not associated with improvements in cognition (214). Nonetheless, the interest in reducing oxidative stress in the brain is justified as a treatment approach because this type of injury could, at the very least, serve as a co-factor mediating AD progression. Potential approaches to reduce oxidative stress include the use of anti-oxidants, anti-inflammatory agents, radical scavengers, transition metal chelators, and non-vitamin anti-oxidant polyphenols (Table 1).

7.5.1. Non-steroidal anti-inflammatory drugs (NSAIDs)

Epidemiologic studies demonstrated an apparently reduced risk of developing AD in ApoE-ε4+ subjects that had been treated chronically with NSAIDs. Therefore, it was proposed that NSAIDs might be effective for treating AD, or preventing AD development in patients with MCI (136, 215-218). These concepts are supported by

the known neuro-inflammatory responses that occur early in the course of AD, and contribute to AßPP-Aß deposition (219). In addition, experimentally, neuro-inflammation leads to recruitment and activation of microglia and astrocytes, which mediate AßPP-Aß deposition (220). However, in clinical trials, selective cyclooxygenase-2 (COX-2) inhibitor drug therapy proved to be ineffective for treating AD (216, 217), or in protecting individuals with MCI from progressing toward AD (217). Therefore, it seems unlikely that this avenue of therapy will help to significantly modify the course of AD.

7.5.2. Radical scavengers

Epidemiological studies suggested that long-term treatment with vitamin E, estrogens, or 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors (statins) may either help prevent dementia, or improve clinical outcomes (194). Interest in the role of estrogens was inspired by the findings that, estrogens stimulate cognitive performance in animal models and, bio-available estrogen declines with aging (221, 222). A few clinical studies have shown limited, short-term benefits of estrogen therapy with regard to cognition (222), but other better controlled trials demonstrated that exogenous estrogen therapy does not improve dementia symptoms in women with AD, and instead, it increases dementia risk when estrogen treatment is begun after age 65 (223, 224). On the other hand, the recent evidence that estrogen receptor modulation therapy may improve cognition (221, 225) deserves further study.

Statins are HMG-CoA reductase inhibitors. HMG-CoA catalyzes the rate-limiting step in cholesterol biosynthesis. In AD, perturbations in cholesterol metabolism and transport contribute to AßPP-Aß deposition and tau hyper-phosphorylation (226, 227), and cerebrovascular disease, which contributes to vascular dementia and AD progression, is associated with hypercholesterolemia. Statin therapy has been evaluated in several clinical trials. Meta-analysis of several large prospective clinical trials revealed no significant benefits of atorvastatin or simvastatin therapy in patients with dementia who had been treated for periods ranging from 26 to 72 weeks, despite significant reductions in serum low density lipoprotein (LDL) (228-231). Still, other studies showed significant reductions in incident dementia among statin users (232, 233). Experimental data suggest that statins may provide some degree of neuroprotection (234).

In an anti-inflammatory treatment prevention trial, despite a 67% reduction in hazard risk of incident AD in subjects treated with lipid-lowering drugs, the most significant findings were that HDL was positively correlated with mini-mental state examination (MMSE) performance, and while LDL cholesterol was negatively correlated with immediate and delayed recall (235). Limitations of this study include its relatively short duration of follow-up and the lack of distinction between vascular dementia and AD. However, the impact of statin therapy was most likely due to reduced severity of cerebrovascular disease, lessening its contribution to AD progression. Recent concerns over the use of statins to treat AD were raised by the findings that: 1) brain cholesterol levels are reduced in AD (227); 2) reductions in neuronal cholesterol lead to impaired insulin signaling and energy metabolism (110); and 3) cognitive impairment can occur with chronic statin use (236-239) and following its discontinuation, cognitive function may be restored (237, 239). Therefore, routine, "preventive" use of statin therapy, particularly in the elderly, should be re-evaluated (240) and perhaps avoided unless indicated for cardiovascular health. Moreover, future studies should assess risk for further cognitive impairment among individuals with AD who do not have hyperlipidemia or cerebrovascular disease.

7.5.3. Transition metal ion chelators

One hypothesis that remains viable is that transition metal ions, including Al (III), Fe (III), Zn (II), and Cu (II), cause neurotoxicity and neurodegeneration (241-243), including in the earliest stages of AD (244). Excess accumulation of transition metal ions promotes oxidative stress, apoptosis, and aggregation and fibrillarization of hyper-phosphorylated tau (245) and AßPP-Aß42 (243, 246). Oxidative stress is mediated by the formation of hydroxyl radicals following interactions between iron and hydrogen peroxide. In AD, brain levels of free heme and hemin are significantly elevated (247), and probably contribute to neurodegeneration by inhibiting cholinergic function, altering AßPP-Aß metabolism, binding to hyper-phosphorylated tau and promoting tau aggregation into paired-helical filaments, and inducing formation of free radicals (247).

Chelation therapy with compounds such as desferrioxamine, Feralex-G, or Clioquinol affords neuroprotection by preventing the aggregation and fibrillarization of AßPP-Aß and tau, and reducing ROS production (245, 248-250). Correspondingly, Clioquinol chelation reduces AßPP-Aß burden in transgenic mice (248, 249). In addition to its proposed direct anti-aggregation effects on AßPP-Aß, chelation therapy could reduce AßPP-Aß deposition by decreasing oxidative stress and ROS (134) caused by heme and heavy metals. Chelation therapy for AD was tested in a 2-year randomized placebo-controlled trial of twice daily injections of the trivalent chelator, desferrioxamine. The rates of performance decline in patients with probable AD slowed (251). However, in a later uncontrolled clinical trial of Clioquinol therapy, AD subjects showed only modest improvements (250). Only a few studies have linked chelation therapy to improved glucose utilization, energy metabolism, and insulin signaling in the brain. Nonetheless, the findings that chelation of zinc and iron prevents or attenuates streptozocin-, alloxan-, or ferritin-induced diabetes (252-254), and that desferrioxamine chelation of iron, and dietary restriction of iron increase glucose uptake and insulin signaling in hepatocytes (255, 256) are intriguing with respect to the roles of brain insulin resistance and metabolic dysfunction in the pathogenesis of AD and neurodegeneration. Since treatment with antioxidants, Vitamin E, Vitamin C, Heme oxygenase 1, or metal chelators prevents the neurotoxic effects of heme and hemin (257), and may also enhance insulin signaling and

glucose utilization in the brain, heme-induced oxidative stress could potentially be targeted by anti-oxidant and chelation therapy to help restore cholinergic function, reduce fibrillarization of tau and AßPP-Aß42, decrease oxidative stress, and improve energy metabolism in the brain.

Despite probable benefits, a major limitation of our current methods of chelation therapy is that delivery of drugs with high Fe (III) binding capacity to the CNS are suboptimal (258, 259). Another point is that liberal use of chelation therapy may deplete iron, which is needed to generate energy, and copper, manganese, and zinc, which participate in enzymatic pathways that protect cells from free radicals and reactive oxygen species through activation of superoxide dismutases I-III. To address these problems, new compounds have been developed and tested in pre-clinical models. For example, DP-109 is a lipophilic metal chelator that reduces cerebral AßPP-Aß burden in Tg2576 transgenic mice (260). Another approach may be to conjugate chelators to nanoparticles that can cross the blood-brain barrier to chelate metal ions, and then exit to remove them (261-263). Recently, Nano-N2PY, a prototype nanoparticle-chelator conjugate was demonstrated to inhibit AßPP-Aß aggregation and reduce AßPP-Aß-associated cortical neuron toxicity in vivo (264). Another novel approach involved the development of site-activated multifunctional chelators, such as HLA20A, that become activated by binding and inhibiting acetylcholinesterase, resulting in the release of an active chelator that reduces AßPP-Aß fibrillization and oxidative stress (265, 266). Along related lines, dual target-directed 1,3-diphenylurea derivatives seem capable of both inhibiting BACE1 and chelating metal ions (267).

7.5.4. Polyphenols

Epidemiological studies demonstrated relative protection from dementia, AD, and Parkinson's disease in populations that regularly consumed green tea or red wine (268). Resveratrol, 3.4',5-trihydroxy-trans-stilbene, is a natural polyphenol that is abundantly present in red wine and has antioxidant and neuroprotective activities. Grape seed extracts also contain resveratrol, and therefore provide neuroprotection (269, 270). Pharmacokinetic studies have affirmed that grape seed polyphenols abundantly distribute in the brain (271). The neuroprotective actions of resveratrol are mediated by enhancement of glutathione free radical scavenger activity (272, 273), and reduction in AßPP-Aß levels (274) due to increased clearance via the proteasome (275) or autophagy and lysosomal degradation (276). Resveratrol also exerts cytoprotective effects by stimulating heme oxygenase, and modulating cellular resistance blood flow, injury, and inflammation (277). In addition, resveratrol and other polyphenols function as metal chelators, and thereby protect the brain from oxidative stress and ROS caused by accumulations of lead, iron, aluminum, zinc, and copper (278).

One critical therapeutic effect of resveratrol is its ability to retard aging and protect against AD due to stimulation of the sirtuin protein, SIRT1 (279). Sirtuin genes promote longevity, and SIRT1-mediated deacetylase activity protects against AD-type neurodegeneration (280, 281). Mechanistically, SIRT1 functions by interfering with AßPP-Aß peptide generation (280, 281), and SIRT1-activating molecules such as resveratrol, reduce neurodegeneration and prevent learning impairments in the p25 transgenic mouse model of AD, which is associated with tau hyper-phosphorylation and fibrillarization (282). Of note is that SIRT1 activation achieves the same effect as caloric restriction with respect to preventing aging and AD (283). Caloric restriction with weight loss is a well-established means of increasing insulin sensitivity (284).

The major green tea polyphenolic compound, epigallocatechin-3-gallate (EGCG), has neuroprotective actions similar to resveratrol. Studies have shown that EGCG: 1) mimics cellular effects of insulin, reducing gluconeogenesis and corresponding enzyme gene expression (285); 2) reduces AßPP-Aß levels by enhancing cleavage and clearance of the C-terminal fragment of AßPP (286); 3) functions as an iron chelating and mitochondrial stabilization compound (287, 288). Moreover, clinical trials have demonstrated that EGCG has neuroprotective and anti-oxidant therapeutic effects in AD, as well as Parkinson's disease (286, 288). To circumvent problems related to dosing and CNS delivery, nanolipidica EGCG particles have been generated and already shown to improve brain distribution following oral administration (289).

8. CONCLUSIONS

Recent literature concerning the roles of brain insulin and IGF resistance and deficiency in the pathogenesis of AD, and the likely mediators of brain insulin/IGF resistance and deficiency is reviewed. Based on human and experimental animal model data generated in various laboratories and institutions, the common theme that ties together nearly all of the pathophysiological abnormalities in AD, from early to late stages, is insulin and IGF resistance. The attendant inhibition of insulin/IGF signaling leads to aberrant activation of kinases that lead to tau hyper-phosphorylation. Impairments in energy metabolism and glucose utilization have broad consequences due to increased oxidative stress, activation of pro-inflammatory cascades, and ROS generation, all of which promote aberrant AßPP expression and cleavage, AßPP-Aß42 accumulation, and fibrillarization and misfolding of tau and AßPP-Aß. Increased ROS causes electrophilic attacks on proteins, lipids, and nucleic acids, resulting in the formation of adducts that promote further structural and functional damage, oxidative stress, ubiquitination of proteins, targeting them for degradation. Insulin/IGF resistance impairs lipid metabolism, leading to disruption of myelin homeostasis. AD also results in white matter atrophy, myelin loss, and increased myelin breakdown with generation of potentially toxic sphingolipids, including ceramides. Neurotoxic ceramides promote insulin resistance, neuroinflammation, and oxidative stress. Finally, brain insulin/IGF resistance can also explain the frequent co-existence of cerebral microvascular disease, which substantially contributes to the neuropathology of AD. Given the multi-step/multi-

tiered problems caused by or associated with brain insulin/IGF resistance, treatment approaches should target AD at multiple levels, and multiple targets over a prolonged period (290, 291), similar to our current approaches for treating malignancies. Future multi-modal therapies for AD should be directed at multiple levels of within the insulin/IGF signaling cascade, beginning with receptor sensitizers, agents to promote insulin synthesis and release, e.g. GLP-1, inhibitors of oxidative stress, radical formation, and metal ion accumulation, tau phosphorylating kinase modulators, and co-factors that support glucose utilization, mitochondrial function, and energy metabolism. If effective, these combined treatments will likely enhance neurotransmitter activity and availability, neuronal plasticity, and neuronal survival, which are needed to preserve cognitive function.

9. ACKNOWLEDGEMENTS

Research was supported by AA11431, AA12908 and AA16260 from the National Institutes of Health.

10. REFERENCES

1. D. M. Walsh, I. Klyubin, J. V. Fadeeva, W. K. Cullen, R. Anwyl, M. S. Wolfe, M. J. Rowan and D. J. Selkoe: Naturally secreted oligomers of amyloid-ß protein potently inhibit hippocampal long-term potentiation in vivo. *Nature*, 416(6880), 535-9 (2002)

2. L. Frolich, D. Blum-Degen, H. G. Bernstein, S. Engelsberger, J. Humrich, S. Laufer, D. Muschner, A. Thalheimer, A. Turk, S. Hoyer, R. Zochling, K. W. Boissl, K. Jellinger and P. Riederer: Brain insulin and insulin receptors in aging and sporadic Alzheimer's disease. *J Neural Transm*, 105(4-5), 423-38 (1998)

3. S. Hoyer: The brain insulin signal transduction system and sporadic (type II) Alzheimer disease: an update. *J Neural Transm*, 109(3), 341-60 (2002)

4. S. Hoyer: Glucose metabolism and insulin receptor signal transduction in Alzheimer disease. *Eur J Pharmacol*, 490(1-3), 115-25 (2004)

5. E. J. Rivera, A. Goldin, N. Fulmer, R. Tavares, J. R. Wands and S. M. de la Monte: Insulin and insulin-like growth factor expression and function deteriorate with progression of Alzheimer's disease: link to brain reductions in acetylcholine. *J Alzheimers Dis*, 8(3), 247-68 (2005)

6. E. Steen, B. M. Terry, E. J. Rivera, J. L. Cannon, T. R. Neely, R. Tavares, X. J. Xu, J. R. Wands and S. M. de la Monte: Impaired insulin and insulin-like growth factor expression and signaling mechanisms in Alzheimer's disease--is this type 3 diabetes? *J Alzheimers Dis*, 7(1), 63-80 (2005)

7. R. Adolfsson, G. Bucht, F. Lithner and B. Winblad: Hypoglycemia in Alzheimer's disease. *Acta Med Scand*, 208(5), 387-8 (1980)

8. Y. Fujisawa, K. Sasaki and K. Akiyama: Increased insulin levels after OGTT load in peripheral blood and cerebrospinal fluid of patients with dementia of Alzheimer type. *Biol Psychiatry*, 30(12), 1219-28 (1991)

R. J. Caselli, K. Chen, W. Lee, G. E. Alexander and E. M. Reiman: Correlating cerebral hypometabolism with future memory decline in subsequent converters to amnestic pre-mild cognitive impairment. *Arch Neurol*, 65(9), 1231-6 (2008)

L. Mosconi, A. Pupi and M. J. De Leon: Brain glucose hypometabolism and oxidative stress in preclinical Alzheimer's disease. *Ann N Y Acad Sci*, 1147, 180-95 (2008)

11. L. Mosconi, R. Mistur, R. Switalski, W. H. Tsui, L. Glodzik, Y. Li, E. Pirraglia, S. De Santi, B. Reisberg, T. Wisniewski and M. J. de Leon: FDG-PET changes in brain glucose metabolism from normal cognition to pathologically verified Alzheimer's disease. *Eur J Nucl Med Mol Imaging*, 36(5), 811-22 (2009)

12. J. B. Langbaum, K. Chen, R. J. Caselli, W. Lee, C. Reschke, D. Bandy, G. E. Alexander, C. M. Burns, A. W. Kaszniak, S. A. Reeder, J. J. Corneveaux, A. N. Allen, J. Pruzin, M. J. Huentelman, A. S. Fleisher and E. M. Reiman: Hypometabolism in Alzheimer-affected brain regions in cognitively healthy Latino individuals carrying the apolipoprotein E ε4 allele. *Arch Neurol*, 67(4), 462-8 (2010)

13. S. Hoyer and R. Nitsch: Cerebral excess release of neurotransmitter amino acids subsequent to reduced cerebral glucose metabolism in early-onset dementia of Alzheimer type. *J Neural Transm*, 75(3), 227-32 (1989)

14. S. Hoyer, R. Nitsch and K. Oesterreich: Predominant abnormality in cerebral glucose utilization in late-onset dementia of the Alzheimer type: a cross-sectional comparison against advanced late-onset and incipient early-onset cases. *J Neural Transm Park Dis Dement Sect*, 3(1), 1-14 (1991)

15. E. Grunblatt, M. Salkovic-Petrisic, J. Osmanovic, P. Riederer and S. Hoyer: Brain insulin system dysfunction in streptozotocin intracerebroventricularly treated rats generates hyperphosphorylated tau protein. *J Neurochem*, 101(3), 757-70 (2007)

16. S. Hoyer, S. K. Lee, T. Loffler and R. Schliebs: Inhibition of the neuronal insulin receptor. An in vivo model for sporadic Alzheimer disease? *Ann N Y Acad Sci*, 920, 256-8 (2000)

17. M. Labak, T. Foniok, D. Kirk, D. Rushforth, B. Tomanek, A. Jasinski and P. Grieb: Metabolic changes in rat brain following intracerebroventricular injections of streptozotocin: a model of sporadic Alzheimer's disease. *Acta Neurochir Suppl*, 106, 177-81 (2010)

18. H. Lannert and S. Hoyer: Intracerebroventricular administration of streptozotocin causes long-term diminutions in learning and memory abilities and in cerebral energy metabolism in adult rats. *Behav Neurosci*, 112(5), 1199-208 (1998)

19. N. Lester-Coll, E. J. Rivera, S. J. Soscia, K. Doiron, J. R. Wands and S. M. de la Monte: Intracerebral streptozotocin model of type 3 diabetes: relevance to sporadic Alzheimer's disease. *J Alzheimers Dis*, 9(1), 13-33 (2006)

20. J. P. Blass, G. E. Gibson and S. Hoyer: The role of the metabolic lesion in Alzheimer's disease. *J Alzheimers Dis*, 4(3), 225-32 (2002)

21. D. Blum-Degen, L. Frolich, S. Hoyer and P. Riederer: Altered regulation of brain glucose metabolism as a cause of neurodegenerative disorders? *J Neural Transm Suppl*, 46, 139-47 (1995)

22. S. Hoyer: Causes and consequences of disturbances of cerebral glucose metabolism in sporadic Alzheimer disease: therapeutic implications. *Adv Exp Med Biol*, 541, 135-52 (2004)

23. C. Qiu, D. De Ronchi and L. Fratiglioni: The epidemiology of the dementias: an update. *Curr Opin Psychiatry*, 20(4), 380-5 (2007)

24. S. Craft, S. Asthana, D. G. Cook, L. D. Baker, M. Cherrier, K. Purganan, C. Wait, A. Petrova, S. Latendresse, G. S. Watson, J. W. Newcomer, G. D. Schellenberg and A. J. Krohn: Insulin dose-response effects on memory and plasma amyloid precursor protein in Alzheimer's disease: interactions with apolipoprotein E genotype. *Psychoneuroendocrinology*, 28(6), 809-22 (2003)

25. S. Craft, S. Asthana, G. Schellenberg, L. Baker, M. Cherrier, A. A. Boyt, R. N. Martins, M. Raskind, E. Peskind and S. Plymate: Insulin effects on glucose metabolism, memory, and plasma amyloid precursor protein in Alzheimer's disease differ according to apolipoprotein-E genotype. *Ann N Y Acad Sci*, 903, 222-8 (2000)

26. S. M. de la Monte and J. R. Wands: Review of insulin and insulin-like growth factor expression, signaling, and malfunction in the central nervous system: relevance to Alzheimer's disease. *J Alzheimers Dis*, 7(1), 45-61 (2005)

27. W. Farris, S. Mansourian, M. A. Leissring, E. A. Eckman, L. Bertram, C. B. Eckman, R. E. Tanzi and D. J. Selkoe: Partial loss-of-function mutations in insulin-degrading enzyme that induce diabetes also impair degradation of amyloid-ß-protein. *Am J Pathol*, 164(4), 1425-34 (2004)

28. M. Schubert, D. P. Brazil, D. J. Burks, J. A. Kushner, J. Ye, C. L. Flint, J. Farhang-Fallah, P. Dikkes, X. M. Warot, C. Rio, G. Corfas and M. F. White: Insulin receptor substrate-2 deficiency impairs brain growth and promotes tau phosphorylation. *J Neurosci*, 23(18), 7084-92 (2003)

29. M. Schubert, D. Gautam, D. Surjo, K. Ueki, S. Baudler, D. Schubert, T. Kondo, J. Alber, N. Galldiks, E. Kustermann, S. Arndt, A. H. Jacobs, W. Krone, C. R. Kahn and J. C. Bruning: Role for neuronal insulin resistance in neurodegenerative diseases. *Proc Natl Acad Sci U S A*, 101(9), 3100-5 (2004)

30. S. Craft: Insulin resistance and cognitive impairment: a view through the prism of epidemiology. *Arch Neurol*, 62(7), 1043-4 (2005)

31. S. Craft: Insulin resistance syndrome and Alzheimer disease: pathophysiologic mechanisms and therapeutic implications. *Alzheimer Dis Assoc Disord*, 20(4), 298-301 (2006)

32. S. Craft: Insulin resistance and Alzheimer's disease pathogenesis: potential mechanisms and implications for treatment. *Curr Alzheimer Res*, 4(2), 147-52 (2007)

33. S. M. de la Monte, M. Tong, N. Lester-Coll, M. Plater, Jr. and J. R. Wands: Therapeutic rescue of neurodegeneration in experimental type 3 diabetes: relevance to Alzheimer's disease. *J Alzheimers Dis*, 10(1), 89-109 (2006)

34. S. M. de la Monte, A. Neusner, J. Chu and M. Lawton: Epidemilogical Trends Strongly Suggest Exposures as Etiologic Agents in the Pathogenesis of Sporadic Alzheimer's Disease, Diabetes Mellitus, and Non-Alcoholic Steatohepatitis. *J Alzheimers Dis* (2009)

35. F. Pasquier, A. Boulogne, D. Leys and P. Fontaine: Diabetes mellitus and dementia. Diabetes Metab, 32(5 Pt 1), 403-14 (2006)

36. A. Verdelho, S. Madureira, J. M. Ferro, A. M. Basile, H. Chabriat, T. Erkinjuntti, F. Fazekas, M. Hennerici, J. O'Brien, L. Pantoni, E. Salvadori, P. Scheltens, M. C. Visser, L. O. Wahlund, G. Waldemar, A. Wallin and D. Inzitari: Differential impact of cerebral white matter changes, diabetes, hypertension and stroke on cognitive performance among non-disabled elderly. The LADIS study. J Neurol Neurosurg Psychiatry, 78(12), 1325-30 (2007)

37. I. J. Martins, E. Hone, J. K. Foster, S. I. Sunram-Lea, A. Gnjec, S. J. Fuller, D. Nolan, S. E. Gandy and R. N. Martins: Apolipoprotein E, cholesterol metabolism, diabetes, and the convergence of risk factors for Alzheimer's disease and cardiovascular disease. Mol Psychiatry, 11(8), 721-36 (2006)

38. M. N. Haan and R. Wallace: Can dementia be prevented? Brain aging in a population-based context. Annu Rev Public Health, 25, 1-24 (2004)

39. L. J. Launer: Diabetes and brain aging: epidemiologic evidence. *Curr Diab Rep*, 5(1), 59-63 (2005)

40. J. A. Luchsinger and R. Mayeux: Cardiovascular risk factors and Alzheimer's disease. *Curr Atheroscler Rep*, 6(4), 261-6 (2004)

41. J. A. Luchsinger, C. Reitz, B. Patel, M. X. Tang, J. J. Manly and R. Mayeux: Relation of diabetes to mild cognitive impairment. *Arch Neurol*, 64(4), 570-5 (2007)

42. R. A. Whitmer: Type 2 diabetes and risk of cognitive impairment and dementia. *Curr Neurol Neurosci Rep*, 7(5), 373-80 (2007)

43. M. Ristow: Neurodegenerative disorders associated with diabetes mellitus. *J Mol Med*, 82(8), 510-29 (2004)

44. R. A. Whitmer, E. P. Gunderson, C. P. Quesenberry, Jr., J. Zhou and K. Yaffe: Body mass index in midlife and risk of Alzheimer disease and vascular dementia. *Curr Alzheimer Res*, 4(2), 103-9 (2007)

45. P. T. Nelson, C. D. Smith, E. A. Abner, F. A. Schmitt, S. W. Scheff, G. J. Davis, J. N. Keller, G. A. Jicha, D. Davis, W. Wang-Xia, A. Hartman, D. G. Katz and W. R. Markesbery: Human cerebral neuropathology of Type 2 diabetes mellitus. *Biochim Biophys Acta* (2008)

46. J. Janson, T. Laedtke, J. E. Parisi, P. O'Brien, R. C. Petersen and P. C. Butler: Increased risk of type 2 diabetes in Alzheimer disease. *Diabetes*, 53(2), 474-81 (2004)

47. G. Winocur and C. E. Greenwood: Studies of the effects of high fat diets on cognitive function in a rat model. *Neurobiol Aging*, 26 Suppl 1, 46-9 (2005)

48. G. Winocur, C. E. Greenwood, G. G. Piroli, C. A. Grillo, L. R. Reznikov, L. P. Reagan and B. S. McEwen: Memory impairment in obese Zucker rats: an investigation of cognitive function in an animal model of insulin resistance and obesity. *Behav Neurosci*, 119(5), 1389-95 (2005)

49. N. Moroz, M. Tong, L. Longato, H. Xu and S. M. de la Monte: Limited Alzheimer-type neurodegeneration in experimental obesity and Type 2 diabetes mellitus. *J Alzheimers Dis*, 15(1), 29-44 (2008)

50. L. E. Lyn-Cook, Jr., M. Lawton, M. Tong, E. Silbermann, L. Longato, P. Jiao, P. Mark, J. R. Wands, H. Xu and S. M. de la Monte: Hepatic ceramide may mediate brain insulin resistance and neurodegeneration in type 2 diabetes and non-alcoholic steatohepatitis. *J Alzheimers Dis*, 16(4), 715-29 (2009)

51. J. A. Luchsinger: Type 2 diabetes, related conditions, in relation and dementia: an opportunity for prevention? *J Alzheimers Dis*, 20(3), 723-36 (2010)

52. D. Etiene, J. Kraft, N. Ganju, T. Gomez-Isla, B. Gemelli, B. T. Hyman, E. T. Hedley-Whyte, J. R. Wands and S. M. De La Monte: Cerebrovascular Pathology Contributes to the Heterogeneity of Alzheimer's Disease. *J Alzheimers Dis*, 1(2), 119-134 (1998)

53. K. Huang, C. C. Zou, X. Z. Yang, X. Q. Chen and L. Liang: Carotid intima-media thickness and serum endothelial marker levels in obese children with metabolic syndrome. *Arch Pediatr Adolesc Med*, 164(9), 846-51

54. O. Hotta, Y. Taguma, S. Chiba, K. Sudou, I. Horigome, N. Yusa and T. Furuta: Possible relationship between hyperinsulinemia and glomerular hypertrophy in nephrosclerosis. *Ren Fail*, 18(2), 271-8 (1996)

55. C. C. Haudenschild, W. Van Sickle and A. V. Chobanian: Response of the aorta of the obese Zucker rat to injury. *Arteriosclerosis*, 1(3), 186-91 (1981)

56. T. Kubota, N. Kubota, M. Moroi, Y. Terauchi, T. Kobayashi, K. Kamata, R. Suzuki, K. Tobe, A. Namiki, S. Aizawa, R. Nagai, T. Kadowaki and T. Yamaguchi: Lack of insulin receptor substrate-2 causes progressive neointima formation in response to vessel injury. *Circulation*, 107(24), 3073-80 (2003)

57. P. Kincaid-Smith: Hypothesis: obesity and the insulin resistance syndrome play a major role in end-stage renal failure attributed to hypertension and labelled 'hypertensive nephrosclerosis'. *J Hypertens*, 22(6), 1051-5 (2004)

58. H. Matsumoto, T. Nakao, T. Okada, Y. Nagaoka, H. Iwasawa, R. Tomaru and T. Wada: Insulin resistance contributes to obesity-related proteinuria. *Intern Med*, 44(6), 548-53 (2005)

59. K. S. Schmidt, J. L. Gallo, C. Ferri, T. Giovannetti, N. Sestito, D. J. Libon and P. S. Schmidt: The neuropsychological profile of alcohol-related dementia suggests cortical and subcortical pathology. *Dement Geriatr Cogn Disord*, 20(5), 286-91 (2005)

60. M. D. Kopelman, A. D. Thomson, I. Guerrini and E. J. Marshall: The Korsakoff syndrome: clinical aspects, psychology and treatment. *Alcohol Alcohol*, 44(2), 148-54 (2009)

61. J. E. Elwing, P. J. Lustman, H. L. Wang and R. E. Clouse: Depression, anxiety, and nonalcoholic steatohepatitis. *Psychosom Med*, 68(4), 563-9 (2006)

62. J. M. Loftis, M. Huckans, S. Ruimy, D. J. Hinrichs and P. Hauser: Depressive symptoms in patients with chronic hepatitis C are correlated with elevated plasma levels of interleukin-1ß and tumor necrosis factor-α. *Neurosci Lett*, 430(3), 264-8 (2008)

63. W. Perry, R. C. Hilsabeck and T. I. Hassanein: Cognitive dysfunction in chronic hepatitis C: a review. *Dig Dis Sci*, 53(2), 307-21 (2008)

64. K. Karaivazoglou, K. Assimakopoulos, K. Thomopoulos, G. Theocharis, L. Messinis, G. Sakellaropoulos and C. Labropoulou-Karatza: Neuropsychological function in Greek patients with chronic hepatitis C. *Liver Int*, 27(6), 798-805 (2007)

65. J. J. Weiss and J. M. Gorman: Psychiatric behavioral aspects of comanagement of hepatitis C virus and HIV. *Curr HIV/AIDS Rep*, 3(4), 176-81 (2006)

66. M. Tong, L. Longato and S. M. de la Monte: Early limited nitrosamine exposures exacerbate high fat diet-

mediated type2 diabetes and neurodegeneration. *BMC Endocr Disord*, 10(1), 4 (2010)

67. M. Tong, A. Neusner, L. Longato, M. Lawton, J. R. Wands and S. M. de la Monte: Nitrosamine Exposure Causes Insulin Resistance Diseases: Relevance to Type 2 Diabetes Mellitus, Non-Alcoholic Steatohepatitis, and Alzheimer's Disease. *J Alzheimers Dis* (2009)

68. J. Capeau: Insulin resistance and steatosis in humans. *Diabetes Metab*, 34(6 Pt 2), 649-57 (2008)

69. E. W. Kraegen and G. J. Cooney: Free fatty acids and skeletal muscle insulin resistance. *Curr Opin Lipidol*, 19(3), 235-41 (2008)

70. Y. Kao, J. H. Youson, J. A. Holmes, A. Al-Mahrouki and M. A. Sheridan: Effects of insulin on lipid metabolism of larvae and metamorphosing landlocked sea lamprey, Petromyzon marinus. *Gen Comp Endocrinol*, 114(3), 405-14 (1999)

71. W. L. Holland and S. A. Summers: Sphingolipids, insulin resistance, and metabolic disease: new insights from in vivo manipulation of sphingolipid metabolism. *Endocr Rev*, 29(4), 381-402 (2008)

72. M. Langeveld and J. M. Aerts: Glycosphingolipids and insulin resistance. *Prog Lipid Res* (2009)

73. S. A. Summers: Ceramides in insulin resistance and lipotoxicity. *Prog Lipid Res*, 45(1), 42-72 (2006)

74. G. Arboleda, T. J. Huang, C. Waters, A. Verkhratsky, P. Fernyhough and R. M. Gibson: Insulin-like growth factor-1-dependent maintenance of neuronal metabolism through the phosphatidylinositol 3-kinase-Akt pathway is inhibited by C2-ceramide in CAD cells. *Eur J Neurosci*, 25(10), 3030-8 (2007)

75. C. E. Chalfant, K. Kishikawa, M. C. Mumby, C. Kamibayashi, A. Bielawska and Y. A. Hannun: Long chain ceramides activate protein phosphatase-1 and protein phosphatase-2A. Activation is stereospecific and regulated by phosphatidic acid. *J Biol Chem*, 274(29), 20313-7 (1999)

76. B. Liu, L. M. Obeid and Y. A. Hannun: Sphingomyelinases in cell regulation. *Semin Cell Dev Biol*, 8(3), 311-322 (1997)

77. L. Bryan, T. Kordula, S. Spiegel and S. Milstien: Regulation and functions of sphingosine kinases in the brain. *Biochim Biophys Acta*, 1781(9), 459-66 (2008)

78. J. R. Van Brocklyn: Sphingolipid signaling pathways as potential therapeutic targets in gliomas. *Mini Rev Med Chem*, 7(10), 984-90 (2007)

79. N. A. Bourbon, L. Sandirasegarane and M. Kester: Ceramide-induced inhibition of Akt is mediated through protein kinase Czeta: implications for growth arrest. *J Biol Chem*, 277(5), 3286-92 (2002)

80. E. Hajduch, A. Balendran, I. H. Batty, G. J. Litherland, A. S. Blair, C. P. Downes and H. S. Hundal: Ceramide impairs the insulin-dependent membrane recruitment of protein kinase B leading to a loss in downstream signalling in L6 skeletal muscle cells. *Diabetologia*, 44(2), 173-83 (2001)

81. T. C. Nogueira, G. F. Anhe, C. R. Carvalho, R. Curi, S. Bordin and A. R. Carpinelli: Involvement of phosphatidylinositol-3 kinase/AKT/PKCzeta/lambda pathway in the effect of palmitate on glucose-induced insulin secretion. *Pancreas*, 37(3), 309-15 (2008)

82. D. J. Powell, E. Hajduch, G. Kular and H. S. Hundal: Ceramide disables 3-phosphoinositide binding to the pleckstrin homology domain of protein kinase B (PKB)/Akt by a PKCzeta-dependent mechanism. *Mol Cell Biol*, 23(21), 7794-808 (2003)

83. S. M. de la Monte, L. Longato, M. Tong, S. DeNucci and J. R. Wands: The liver-brain axis of alcohol-mediated neurodegeneration: role of toxic lipids. *Int J Environ Res Public Health*, 6(7), 2055-75 (2009)

84. S. M. de la Monte, M. Tong, V. Nguyen, M. Setshedi, L. Longato and J. R. Wands: Ceramide-mediated insulin resistance and impairment of cognitive-motor functions. *J Alzheimers Dis*, 21(3), 967-84 (2010)

85. S. M. de la Monte, L. Longato, M. Tong and J. R. Wands: Insulin resistance and neurodegeneration: roles of obesity, type 2 diabetes mellitus and non-alcoholic steatohepatitis. *Curr Opin Investig Drugs*, 10(10), 1049-60 (2009)

86. M. Tong and S. M. de la Monte: Mechanisms of ceramide-mediated neurodegeneration. *J Alzheimers Dis*, 16(4), 705-14 (2009)

87. G. Landreth: PPARγ agonists as new therapeutic agents for the treatment of Alzheimer's disease. *Exp Neurol*, 199(2), 245-8 (2006)

88. M. T. Heneka and G. E. Landreth: PPARs in the brain. *Biochim Biophys Acta*, 1771(8), 1031-45 (2007)

89. G. Landreth: Therapeutic use of agonists of the nuclear receptor PPARγ in Alzheimer's disease. *Curr Alzheimer Res*, 4(2), 159-64 (2007)

90. L. Longato, M. Tong, J. R. Wands and S. M. De la Monte: Ex Vivo Model of Steatohepatitis Using Precision-Cut Liver Slice Cultures. *Hepatology*, 52(Supplement 1), 454A (2010)

91. G. Marchesini and R. Marzocchi: Metabolic syndrome and NASH. *Clin Liver Dis*, 11(1), 105-17, ix (2007)

92. M. R. Nicolls: The clinical and biological relationship between Type II diabetes mellitus and

Alzheimer's disease. *Curr Alzheimer Res*, 1(1), 47-54 (2004)

93. D. Papandreou, I. Rousso and I. Mavromichalis: Update on non-alcoholic fatty liver disease in children. *Clin Nutr*, 26(4), 409-15 (2007)

94. D. Pessayre: Role of mitochondria in non-alcoholic fatty liver disease. *J Gastroenterol Hepatol*, 22 Suppl 1, S20-7 (2007)

95. M. M. Yeh and E. M. Brunt: Pathology of nonalcoholic fatty liver disease. *Am J Clin Pathol*, 128(5), 837-47 (2007)

96. M. P. Biju and C. S. Paulose: Brain glutamate dehydrogenase changes in streptozotocin diabetic rats as a function of age. *Biochem Mol Biol Int*, 44(1), 1-7 (1998)

97. S. Hoyer, H. Lannert, M. Noldner and S. S. Chatterjee: Damaged neuronal energy metabolism and behavior are improved by Ginkgo biloba extract (EGb 761). *J Neural Transm*, 106(11-12), 1171-88 (1999)

98. A. Nitta, R. Murai, N. Suzuki, H. Ito, H. Nomoto, G. Katoh, Y. Furukawa and S. Furukawa: Diabetic neuropathies in brain are induced by deficiency of BDNF. *Neurotoxicol Teratol*, 24(5), 695-701 (2002)

99. M. Weinstock and S. Shoham: Rat models of dementia based on reductions in regional glucose metabolism, cerebral blood flow and cytochrome oxidase activity. *J Neural Transm*, 111(3), 347-66 (2004)

100. T. Szkudelski: The mechanism of alloxan and streptozotocin action in B cells of the rat pancreas. *Physiol Res*, 50(6), 537-46 (2001)

101. A. D. Bolzan and M. S. Bianchi: Genotoxicity of streptozotocin. *Mutat Res*, 512(2-3), 121-34 (2002)

102. M. Koulmanda, A. Qipo, S. Chebrolu, J. O'Neil, H. Auchincloss and R. N. Smith: The effect of low versus high dose of streptozotocin in cynomolgus monkeys (Macaca fascilularis). *Am J Transplant*, 3(3), 267-72 (2003)

103. C. Duyckaerts, B. Delatour and M. C. Potier: Classification and basic pathology of Alzheimer disease. *Acta Neuropathol*, 118(1), 5-36 (2009)

104. A. Takashima: Amyloid-ß, tau, and dementia. *J Alzheimers Dis*, 17(4), 729-36 (2009)

105. K. Iqbal, F. Liu, C. X. Gong, C. Alonso Adel and I. Grundke-Iqbal: Mechanisms of tau-induced neurodegeneration. *Acta Neuropathol*, 118(1), 53-69 (2009)

106. A. Takashima: [Drug development for tauopathy and Alzheimer's disease]. *Nihon Shinkei Seishin Yakurigaku Zasshi*, 30(4), 177-80 (2010)

107. S. M. de la Monte, N. Ganju, K. Banerjee, N. V. Brown, T. Luong and J. R. Wands: Partial rescue of ethanol-induced neuronal apoptosis by growth factor activation of phosphoinositol-3-kinase. *Alcohol Clin Exp Res*, 24(5), 716-26 (2000)

108. S. M. de la Monte, T. R. Neely, J. Cannon and J. R. Wands: Ethanol impairs insulin-stimulated mitochondrial function in cerebellar granule neurons. *Cell Mol Life Sci*, 58(12-13), 1950-60. (2001)

109. S. M. de la Monte and J. R. Wands: Chronic gestational exposure to ethanol impairs insulin-stimulated survival and mitochondrial function in cerebellar neurons. *CMLS, Cell Mol Life Sci*, 59, 882-893 (2002)

110. J. Xu, J. Eun Yeon, H. Chang, G. Tison, G. Jun Chen, J. R. Wands and S. M. De La Monte: Ethanol impairs insulin-stimulated neuronal survival in the developing brain: Role of PTEN phosphatase. *J Biol Chem*, 278(29), 26929-37 (2003)

111. B. W. Doble and J. R. Woodgett: GSK-3: tricks of the trade for a multi-tasking kinase. *J Cell Sci*, 116(Pt 7), 1175-86 (2003)

112. G. V. De Ferrari and N. C. Inestrosa: Wnt signaling function in Alzheimer's disease. *Brain Res Brain Res Rev*, 33(1), 1-12 (2000)

113. P. E. Fraser, G. Yu, L. Levesque, M. Nishimura, D. S. Yang, H. T. Mount, D. Westaway and P. H. St George-Hyslop: Presenilin function: connections to Alzheimer's disease and signal transduction. *Biochem Soc Symp*(67), 89-100 (2001)

114. M. Grilli, G. Ferrari Toninelli, D. Uberti, P. Spano and M. Memo: Alzheimer's disease linking neurodegeneration with neurodevelopment. *Funct Neurol*, 18(3), 145-8 (2003)

115. A. Mudher, S. Chapman, J. Richardson, A. Asuni, G. Gibb, C. Pollard, R. Killick, T. Iqbal, L. Raymond, I. Varndell, P. Sheppard, A. Makoff, E. Gower, P. E. Soden, P. Lewis, M. Murphy, T. E. Golde, H. T. Rupniak, B. H. Anderton and S. Lovestone: Dishevelled regulates the metabolism of amyloid precursor protein via protein kinase C/mitogen-activated protein kinase and c-Jun terminal kinase. *J Neurosci*, 21(14), 4987-95 (2001)

116. M. Nishimura, G. Yu, G. Levesque, D. M. Zhang, L. Ruel, F. Chen, P. Milman, E. Holmes, Y. Liang, T. Kawarai, E. Jo, A. Supala, E. Rogaeva, D. M. Xu, C. Janus, L. Levesque, Q. Bi, M. Duthie, R. Rozmahel, K. Mattila, L. Lannfelt, D. Westaway, H. T. Mount, J. Woodgett, P. St George-Hyslop and et al.: Presenilin mutations associated with Alzheimer disease cause defective intracellular trafficking of ß-catenin, a component of the presenilin protein complex. *Nat Med*, 5(2), 164-9 (1999)

117. T. Lebouvier, T. M. Scales, R. Williamson, W. Noble, C. Duyckaerts, D. P. Hanger, C. H. Reynolds, B. H. Anderton and P. Derkinderen: The microtubule-associated protein tau is also phosphorylated on tyrosine. *J Alzheimers Dis*, 18(1), 1-9 (2009)

118. I. Morales, G. Farias and R. B. Maccioni: Neuroimmunomodulation in the pathogenesis of Alzheimer's disease. *Neuroimmunomodulation*, 17(3), 202-4 (2010)

119. D. P. Hanger, A. Seereeram and W. Noble: Mediators of tau phosphorylation in the pathogenesis of Alzheimer's disease. *Expert Rev Neurother*, 9(11), 1647-66 (2009)

120. G. S. Watson, E. R. Peskind, S. Asthana, K. Purganan, C. Wait, D. Chapman, M. W. Schwartz, S. Plymate and S. Craft: Insulin increases CSF Aß42 levels in normal older adults. *Neurology*, 60(12), 1899-903 (2003)

121. L. Gasparini, G. K. Gouras, R. Wang, R. S. Gross, M. F. Beal, P. Greengard and H. Xu: Stimulation of ß-amyloid precursor protein trafficking by insulin reduces intraneuronal ß-amyloid and requires mitogen-activated protein kinase signaling. *J Neurosci*, 21(8), 2561-70 (2001)

122. L. Gasparini, W. J. Netzer, P. Greengard and H. Xu: Does insulin dysfunction play a role in Alzheimer's disease? *Trends Pharmacol Sci*, 23(6), 288-93 (2002)

123. C. Messier and K. Teutenberg: The role of insulin, insulin growth factor, and insulin-degrading enzyme in brain aging and Alzheimer's disease. *Neural Plast*, 12(4), 311-28 (2005)

124. X. Ling, R. N. Martins, M. Racchi, S. Craft and E. Helmerhorst: Amyloid-ß antagonizes insulin promoted secretion of the amyloid-ß protein precursor. *J Alzheimers Dis*, 4(5), 369-74 (2002)

125. L. Xie, E. Helmerhorst, K. Taddei, B. Plewright, W. Van Bronswijk and R. Martins: Alzheimer's ß-amyloid peptides compete for insulin binding to the insulin receptor. *J Neurosci*, 22(10), RC221 (2002)

126. W. H. Zheng, S. Kar, S. Dore and R. Quirion: Insulin-like growth factor-1 (IGF-1): a neuroprotective trophic factor acting via the Akt kinase pathway. *J Neural Transm Suppl*(60), 261-72 (2000)

127. S. Dore, S. Bastianetto, S. Kar and R. Quirion: Protective and rescuing abilities of IGF-I and some putative free radical scavengers against ß-amyloid-inducing toxicity in neurons. *Ann N Y Acad Sci*, 890, 356-64 (1999)

128. S. Dore, S. Kar and R. Quirion: Insulin-like growth factor I protects and rescues hippocampal neurons against ß-amyloid- and human amylin-induced toxicity. *Proc Natl Acad Sci U S A*, 94(9), 4772-7 (1997)

129. G. Evin and A. Weidemann: Biogenesis and metabolism of Alzheimer's disease Aß amyloid peptides. *Peptides*, 23(7), 1285-97 (2002)

130. E. Tsukamoto, Y. Hashimoto, K. Kanekura, T. Niikura, S. Aiso and I. Nishimoto: Characterization of the toxic mechanism triggered by Alzheimer's amyloid-ß peptides via p75 neurotrophin receptor in neuronal hybrid cells. *J Neurosci Res*, 73(5), 627-36 (2003)

131. P. Iwangoff, R. Armbruster, A. Enz and W. Meier-Ruge: Glycolytic enzymes from human autoptic brain cortex: normal aged and demented cases. *Mech Ageing Dev*, 14(1-2), 203-9 (1980)

132. N. R. Sims, D. M. Bowen, C. C. Smith, R. H. Flack, A. N. Davison, J. S. Snowden and D. Neary: Glucose metabolism and acetylcholine synthesis in relation to neuronal activity in Alzheimer's disease. *Lancet*, 1(8164), 333-6 (1980)

133. S. Hoyer and H. Lannert: Inhibition of the neuronal insulin receptor causes Alzheimer-like disturbances in oxidative/energy brain metabolism and in behavior in adult rats. *Ann N Y Acad Sci*, 893, 301-3 (1999)

134. G. J. Chen, J. Xu, S. A. Lahousse, N. L. Caggiano and S. M. de la Monte: Transient hypoxia causes Alzheimer-type molecular and biochemical abnormalities in cortical neurons: potential strategies for neuroprotection. *J Alzheimers Dis*, 5(3), 209-28 (2003)

135. I. Blasko, M. Stampfer-Kountchev, P. Robatscher, R. Veerhuis, P. Eikelenboom and B. Grubeck-Loebenstein: How chronic inflammation can affect the brain and support the development of Alzheimer's disease in old age: the role of microglia and astrocytes. *Aging Cell*, 3(4), 169-76 (2004)

136. P. Eikelenboom and W. A. van Gool: Neuroinflammatory perspectives on the two faces of Alzheimer's disease. *J Neural Transm*, 111(3), 281-94 (2004)

137. E. E. Tuppo and H. R. Arias: The role of inflammation in Alzheimer's disease. *Int J Biochem Cell Biol*, 37(2), 289-305 (2005)

138. A. Lorenzo and B. A. Yankner: Amyloid fibril toxicity in Alzheimer's disease and diabetes. *Ann N Y Acad Sci*, 777, 89-95 (1996)

139. T. Niikura, Y. Hashimoto, H. Tajima and I. Nishimoto: Death and survival of neuronal cells exposed to Alzheimer's insults. *J Neurosci Res*, 70(3), 380-91 (2002)

140. I. Tahirovic, E. Sofic, A. Sapcanin, I. Gavrankapetanovic, L. Bach-Rojecky, M. Salkovic-Petrisic, Z. Lackovic, S. Hoyer and P. Riederer: Reduced brain antioxidant capacity in rat models of ßcytotoxic-induced experimental sporadic Alzheimer's disease and diabetes mellitus. *Neurochem Res*, 32(10), 1709-17 (2007)

141. S. M. de la Monte, M. Tong, N. Bowling and P. Moskal: si-RNA inhibition of brain insulin or insulin-like growth factor receptors causes developmental cerebellar abnormalities: relevance to fetal alcohol spectrum disorder. *Molecular brain*, 4, 13 (2011)

142. S. M. de la Monte and M. Tong: Mechanisms of Nitrosamine-Mediated Neurodegeneration: Potential

Relevance to Sporadic Alzheimer's Disease. *J Alzheimers Dis* (2009)

143. S. M. de la Monte, M. Tong, M. Lawton and L. Longato: Nitrosamine exposure exacerbates high fat diet-mediated type 2 diabetes mellitus, non-alcoholic steatohepatitis, and neurodegeneration with cognitive impairment. *Mol Neurodegener*, 4, 54 (2009)

144. B. J. Boucher, S. W. Ewen and J. M. Stowers: Betel nut (Areca catechu) consumption and the induction of glucose intolerance in adult CD1 mice and in their F1 and F2 offspring. *Diabetologia*, 37(1), 49-55 (1994)

145. G. Dahlquist: Non-genetic risk determinants of type 1 diabetes. *Diabete & metabolisme*, 20(3), 251-7 (1994)

146. G. G. Dahlquist, L. G. Blom, L. A. Persson, A. I. Sandstrom and S. G. Wall: Dietary factors and the risk of developing insulin dependent diabetes in childhood. *BMJ*, 300(6735), 1302-6 (1990)

147. G. S. Watson, T. Bernhardt, M. A. Reger, B. A. Cholerton, L. D. Baker, E. R. Peskind, S. Asthana, S. R. Plymate, L. Frolich and S. Craft: Insulin effects on CSF norepinephrine and cognition in Alzheimer's disease. *Neurobiol Aging*, 27(1), 38-41 (2006)

148. D. Galasko: Insulin and Alzheimer's disease: an amyloid connection. *Neurology*, 60(12), 1886-7 (2003)

149. M. A. Reger, G. S. Watson, P. S. Green, L. D. Baker, B. Cholerton, M. A. Fishel, S. R. Plymate, M. M. Cherrier, G. D. Schellenberg, W. H. Frey, 2nd and S. Craft: Intranasal insulin administration dose-dependently modulates verbal memory and plasma amyloid-ß in memory-impaired older adults. *J Alzheimers Dis*, 13(3), 323-31 (2008)

150. M. A. Reger, G. S. Watson, P. S. Green, C. W. Wilkinson, L. D. Baker, B. Cholerton, M. A. Fishel, S. R. Plymate, J. C. Breitner, W. Degroodt, P. Mehta and S. Craft: Intranasal insulin improves cognition and modulates {ß}-amyloid in early AD. *Neurology*, 70(6), 440-8 (2008)

151. T. Perry and N. H. Greig: Enhancing central nervous system endogenous GLP-1 receptor pathways for intervention in Alzheimer's disease. *Curr Alzheimer Res*, 2(3), 377-85 (2005)

152. L. Li: Is Glucagon-like peptide-1, an agent treating diabetes, a new hope for Alzheimer's disease? *Neurosci Bull*, 23(1), 58-65 (2007)

153. J. Liu, F. Yin, X. Zheng, J. Jing and Y. Hu: Geniposide, a novel agonist for GLP-1 receptor, prevents PC12 cells from oxidative damage via MAP kinase pathway. *Neurochem Int*, 51(6-7), 361-9 (2007)

154. S. C. Biswas, J. Buteau and L. A. Greene: Glucagon-like peptide-1 (GLP-1) diminishes neuronal degeneration and death caused by NGF deprivation by suppressing Bim induction. *Neurochem Res*, 33(9), 1845-51 (2008)

155. J. H. Liu, F. Yin, L. X. Guo, X. H. Deng and Y. H. Hu: Neuroprotection of geniposide against hydrogen peroxide induced PC12 cells injury: involvement of PI3 kinase signal pathway. *Acta Pharmacol Sin*, 30(2), 159-65 (2009)

156. M. D'Amico, C. Di Filippo, R. Marfella, A. M. Abbatecola, F. Ferraraccio, F. Rossi and G. Paolisso: Long-term inhibition of dipeptidyl peptidase-4 in Alzheimer's prone mice. *Exp Gerontol*, 45(3), 202-7 (2010)

157. C. Holscher: Incretin analogues that have been developed to treat type 2 diabetes hold promise as a novel treatment strategy for Alzheimer's disease. *Recent Pat CNS Drug Discov*, 5(2), 109-17 (2010)

158. T. Perry, N. J. Haughey, M. P. Mattson, J. M. Egan and N. H. Greig: Protection and reversal of excitotoxic neuronal damage by glucagon-like peptide-1 and exendin-4. *J Pharmacol Exp Ther*, 302(3), 881-8 (2002)

159. P. L. McClean, V. A. Gault, P. Harriott and C. Holscher: Glucagon-like peptide-1 analogues enhance synaptic plasticity in the brain: a link between diabetes and Alzheimer's disease. *Eur J Pharmacol*, 630(1-3), 158-62 (2010)

160. A. Harkavyi and P. S. Whitton: Glucagon-like peptide 1 receptor stimulation as a means of neuroprotection. *Br J Pharmacol*, 159(3), 495-501 (2010)

161. C. Holscher and L. Li: New roles for insulin-like hormones in neuronal signalling and protection: new hopes for novel treatments of Alzheimer's disease? *Neurobiol Aging*, 31(9), 1495-502 (2010)

162. Y. H. Ma, Y. Zhang, L. Cao, J. C. Su, Z. W. Wang, A. B. Xu and S. C. Zhang: Effect of neurotrophin-3 genetically modified olfactory ensheathing cells transplantation on spinal cord injury. *Cell Transplant*, 19(2), 167-77 (2010)

163. K. Wakabayashi, A. Nagai, A. M. Sheikh, Y. Shiota, D. Narantuya, T. Watanabe, J. Masuda, S. Kobayashi, S. U. Kim and S. Yamaguchi: Transplantation of human mesenchymal stem cells promotes functional improvement and increased expression of neurotrophic factors in a rat focal cerebral ischemia model. *J Neurosci Res*, 88(5), 1017-25 (2010)

164. J. Liu, Z. Zhang, J. T. Li, Y. H. Zhu, H. L. Zhou, S. Liu and T. H. Wang: Effects of NT-4 gene modified fibroblasts transplanted into AD rats. *Neurosci Lett*, 466(1), 1-5 (2009)

165. A. M. Heile, C. Wallrapp, P. M. Klinge, A. Samii, M. Kassem, G. Silverberg and T. Brinker: Cerebral transplantation of encapsulated mesenchymal stem cells

improves cellular pathology after experimental traumatic brain injury. *Neurosci Lett*, 463(3), 176-81 (2009)

166. S. Correia, C. Carvalho, M. S. Santos, R. Seica, C. R. Oliveira and P. I. Moreira: Mechanisms of action of metformin in type 2 diabetes and associated complications: an overview. *Mini Rev Med Chem*, 8(13), 1343-54 (2008)

167. Y. Chen, K. Zhou, R. Wang, Y. Liu, Y. D. Kwak, T. Ma, R. C. Thompson, Y. Zhao, L. Smith, L. Gasparini, Z. Luo, H. Xu and F. F. Liao: Antidiabetic drug metformin (GlucophageR) increases biogenesis of Alzheimer's amyloid peptides via up-regulating BACE1 transcription. *Proc Natl Acad Sci U S A*, 106(10), 3907-12 (2009)

168. R. K. Kaundal and S. S. Sharma: Peroxisome proliferator-activated receptor-γ agonists as neuroprotective agents. *Drug News Perspect*, 23(4), 241-56 (2010)

169. J. C. Strum, R. Shehee, D. Virley, J. Richardson, M. Mattie, P. Selley, S. Ghosh, C. Nock, A. Saunders and A. Roses: Rosiglitazone induces mitochondrial biogenesis in mouse brain. *J Alzheimers Dis*, 11(1), 45-51 (2007)

170. H. Hanyu and T. Sato: [Alzheimer's disease]. *Nippon Rinsho*, 68(2), 330-4 (2010)

171. H. Xu, G. T. Barnes, Q. Yang, G. Tan, D. Yang, C. J. Chou, J. Sole, A. Nichols, J. S. Ross, L. A. Tartaglia and H. Chen: Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *J Clin Invest*, 112(12), 1821-30 (2003)

172. W. A. Pedersen, P. J. McMillan, J. J. Kulstad, J. B. Leverenz, S. Craft and G. R. Haynatzki: Rosiglitazone attenuates learning and memory deficits in Tg2576 Alzheimer mice. *Exp Neurol*, 199(2), 265-73 (2006)

173. M. N. Haan: Therapy Insight: type 2 diabetes mellitus and the risk of late-onset Alzheimer's disease. *Nat Clin Pract Neurol*, 2(3), 159-66 (2006)

174. G. S. Watson, B. A. Cholerton, M. A. Reger, L. D. Baker, S. R. Plymate, S. Asthana, M. A. Fishel, J. J. Kulstad, P. S. Green, D. G. Cook, S. E. Kahn, M. L. Keeling and S. Craft: Preserved cognition in patients with early Alzheimer disease and amnestic mild cognitive impairment during treatment with rosiglitazone: a preliminary study. *Am J Geriatr Psychiatry*, 13(11), 950-8 (2005)

175. M. E. Risner, A. M. Saunders, J. F. Altman, G. C. Ormandy, S. Craft, I. M. Foley, M. E. Zvartau-Hind, D. A. Hosford and A. D. Roses: Efficacy of rosiglitazone in a genetically defined population with mild-to-moderate Alzheimer's disease. *Pharmacogenomics J*, 6(4), 246-54 (2006)

176. M. Gold, C. Alderton, M. Zvartau-Hind, S. Egginton, A. M. Saunders, M. Irizarry, S. Craft, G. Landreth, U. Linnamagi and S. Sawchak: Rosiglitazone monotherapy in mild-to-moderate alzheimer's disease: results from a randomized, double-blind, placebo-controlled phase III study. *Dement Geriatr Cogn Disord*, 30(2), 131-46 (2010)

177. G. Medina-Gomez, S. Gray and A. Vidal-Puig: Adipogenesis and lipotoxicity: role of peroxisome proliferator-activated receptor γ (PPARγ) and PPARγcoactivator-1 (PGC1). *Public Health Nutr*, 10(10A), 1132-7 (2007)

178. S. Crunkhorn and M. E. Patti: Links between thyroid hormone action, oxidative metabolism, and diabetes risk? *Thyroid*, 18(2), 227-37 (2008)

179. B. M. Spiegelman: Transcriptional control of mitochondrial energy metabolism through the PGC1 coactivators. *Novartis Found Symp*, 287, 60-3; discussion 63-9 (2007)

180. K. Rona-Voros and P. Weydt: The role of PGC-1α in the pathogenesis of neurodegenerative disorders. *Curr Drug Targets*, 11(10), 1262-9 (2010)

181. R. V. Bhat, S. L. Budd Haeberlein and J. Avila: Glycogen synthase kinase 3: a drug target for CNS therapies. *J Neurochem*, 89(6), 1313-7 (2004)

JNC2422 [pii]

182. L. Munoz and A. J. Ammit: Targeting p38 MAPK pathway for the treatment of Alzheimer's disease. *Neuropharmacology*, 58(3), 561-8 (2010)

183. C. X. Gong, I. Grundke-Iqbal and K. Iqbal: Targeting tau protein in Alzheimer's disease. *Drugs Aging*, 27(5), 351-65 (2010)

184. J. Avila, F. Wandosell and F. Hernandez: Role of glycogen synthase kinase-3 in Alzheimer's disease pathogenesis and glycogen synthase kinase-3 inhibitors. *Expert Rev Neurother*, 10(5), 703-10 (2010)

185. A. Beauchard, H. Laborie, H. Rouillard, O. Lozach, Y. Ferandin, R. Le Guevel, C. Guguen-Guillouzo, L. Meijer, T. Besson and V. Thiery: Synthesis and kinase inhibitory activity of novel substituted indigoids. *Bioorg Med Chem*, 17(17), 6257-63 (2009)

186. A. Martinez and D. I. Perez: GSK-3 inhibitors: a ray of hope for the treatment of Alzheimer's disease? *J Alzheimers Dis*, 15(2), 181-91 (2008)

187. A. Camins, E. Verdaguer, F. Junyent, M. Yeste-Velasco, C. Pelegri, J. Vilaplana and M. Pallas: Potential mechanisms involved in the prevention of neurodegenerative diseases by lithium. *CNS Neurosci Ther*, 15(4), 333-44 (2009)

188. T. Terao, H. Nakano, Y. Inoue, T. Okamoto, J. Nakamura and N. Iwata: Lithium and dementia: a preliminary study. *Prog Neuropsychopharmacol Biol Psychiatry*, 30(6), 1125-8 (2006)

189. P. V. Nunes, O. V. Forlenza and W. F. Gattaz: Lithium and risk for Alzheimer's disease in elderly patients with bipolar disorder. *Br J Psychiatry*, 190, 359-60 (2007)

190. J. Zhong and W. H. Lee: Lithium: a novel treatment for Alzheimer's disease? *Expert Opin Drug Saf*, 6(4), 375-83 (2007)

191. L. V. Kessing, L. Sondergard, J. L. Forman and P. K. Andersen: Lithium treatment and risk of dementia. *Arch Gen Psychiatry*, 65(11), 1331-5 (2008)

192. H. L. Yeh and S. J. Tsai: Lithium may be useful in the prevention of Alzheimer's disease in individuals at risk of presenile familial Alzheimer's disease. *Med Hypotheses*, 71(6), 948-51 (2008)

193. H. Hampel, M. Ewers, K. Burger, P. Annas, A. Mortberg, A. Bogstedt, L. Frolich, J. Schroder, P. Schonknecht, M. W. Riepe, I. Kraft, T. Gasser, T. Leyhe, H. J. Moller, A. Kurz and H. Basun: Lithium trial in Alzheimer's disease: a randomized, single-blind, placebo-controlled, multicenter 10-week study. *J Clin Psychiatry*, 70(6), 922-31 (2009)

194. M. Hull, M. Berger and M. Heneka: Disease-modifying therapies in Alzheimer's disease: how far have we come? *Drugs*, 66(16), 2075-93 (2006)

195. J. Hardy: The amyloid hypothesis for Alzheimer's disease: a critical reappraisal. *J Neurochem*, 110(4), 1129-34 (2009)

196. C. A. Lemere: Developing novel immunogens for a safe and effective Alzheimer's disease vaccine. *Prog Brain Res*, 175, 83-93 (2009)

197. D. M. Wilcock and C. A. Colton: Immunotherapy, vascular pathology, and microhemorrhages in transgenic mice. *CNS Neurol Disord Drug Targets*, 8(1), 50-64 (2009)

198. V. Vasilevko and E. Head: Immunotherapy in a natural model of Aß pathogenesis: the aging beagle. *CNS Neurol Disord Drug Targets*, 8(2), 98-113 (2009)

199. G. A. Kerchner and A. L. Boxer: Bapineuzumab. *Expert Opin Biol Ther*, 10(7), 1121-30 (2010)

200. D. Boche, N. Denham, C. Holmes and J. A. Nicoll: Neuropathology after active Aß42 immunotherapy: implications for Alzheimer's disease pathogenesis. *Acta Neuropathol*, 120(3), 369-84 (2010)

201. E. Giacobini and R. E. Becker: One hundred years after the discovery of Alzheimer's disease. A turning point for therapy? *J Alzheimers Dis*, 12(1), 37-52 (2007)

202. S. Kuzuhara: [Treatment strategy of Alzheimer's disease: pause in clinical trials of Aß vaccine and next steps]. *Brain Nerve*, 62(7), 659-66 (2010)

203. M. S. Wolfe: Selective amyloid-ß lowering agents. *BMC Neurosci*, 9 Suppl 2, S4 (2008)

204. B. A. Bergmans and B. De Strooper: γ-secretases: from cell biology to therapeutic strategies. *Lancet Neurol*, 9(2), 215-26 (2010)

205. D. B. Henley, P. C. May, R. A. Dean and E. R. Siemers: Development of semagacestat (LY450139), a functional γ-secretase inhibitor, for the treatment of Alzheimer's disease. *Expert Opin Pharmacother*, 10(10), 1657-64 (2009)

206. C. Guardia-Laguarta, M. Pera and A. Lleo: γ-Secretase as a therapeutic target in Alzheimer's disease. *Curr Drug Targets*, 11(4), 506-17 (2010)

207. G. B. Frisoni and A. Delacourte: Neuroimaging outcomes in clinical trials in Alzheimer's disease. *J Nutr Health Aging*, 13(3), 209-12 (2009)

208. S. Krishnaswamy, G. Verdile, D. Groth, L. Kanyenda and R. N. Martins: The structure and function of Alzheimer's γ secretase enzyme complex. *Crit Rev Clin Lab Sci*, 46(5-6), 282-301 (2009)

209. V. Frisardi, V. Solfrizzi, P. B. Imbimbo, C. Capurso, A. D'Introno, A. M. Colacicco, G. Vendemiale, D. Seripa, A. Pilotto, A. Capurso and F. Panza: Towards disease-modifying treatment of Alzheimer's disease: drugs targeting ß-amyloid. *Curr Alzheimer Res*, 7(1), 40-55 (2010)

210. R. M. Costa, C. Drew and A. J. Silva: Notch to remember. *Trends Neurosci*, 28(8), 429-35 (2005)

211. C. E. Augelli-Szafran, H. X. Wei, D. Lu, J. Zhang, Y. Gu, T. Yang, P. Osenkowski, W. Ye and M. S. Wolfe: Discovery of notch-sparing γ-secretase inhibitors. *Curr Alzheimer Res*, 7(3), 207-9 (2010)

212. T. Tomita: [Alzheimer's disease treatment by inhibition/modulation of the γ-secretase activity]. *Rinsho Shinkeigaku*, 49(11), 845-7 (2009)

213. M. W. Marlatt, P. J. Lucassen, G. Perry, M. A. Smith and X. Zhu: Alzheimer's disease: cerebrovascular dysfunction, oxidative stress, and advanced clinical therapies. *J Alzheimers Dis*, 15(2), 199-210 (2008)

214. I. Blasko, S. Jungwirth, K. Jellinger, G. Kemmler, W. Krampla, S. Weissgram, I. Wichart, K. H. Tragl, H. Hinterhuber and P. Fischer: Effects of medications on plasma amyloid-ß (Aß) 42: longitudinal data from the VITA cohort. *J Psychiatr Res*, 42(11), 946-55 (2008)

215. K. P. Townsend and D. Pratico: Novel therapeutic opportunities for Alzheimer's disease: focus on nonsteroidal anti-inflammatory drugs. *Faseb J*, 19(12), 1592-601 (2005)

216. C. A. Szekely and P. P. Zandi: Non-steroidal anti-inflammatory drugs and Alzheimer's disease: the epidemiological evidence. *CNS Neurol Disord Drug Targets*, 9(2), 132-9 (2010)

217. B. P. Imbimbo: An update on the efficacy of non-steroidal anti-inflammatory drugs in Alzheimer's disease. *Expert Opin Investig Drugs*, 18(8), 1147-68 (2009)

218. S. Weggen, M. Rogers and J. Eriksen: NSAIDs: small molecules for prevention of Alzheimer's disease or precursors for future drug development? *Trends Pharmacol Sci*, 28(10), 536-43 (2007)

219. P. B. Rosenberg: Clinical aspects of inflammation in Alzheimer's disease. *Int Rev Psychiatry*, 17(6), 503-14 (2005)

220. M. Sastre, T. Klockgether and M. T. Heneka: Contribution of inflammatory processes to Alzheimer's disease: molecular mechanisms. *Int J Dev Neurosci*, 24(2-3), 167-76 (2006)

221. S. C. Janicki and N. Schupf: Hormonal influences on cognition and risk for Alzheimer's disease. *Curr Neurol Neurosci Rep*, 10(5), 359-66 (2010)

222. V. W. Henderson: Aging, estrogens, and episodic memory in women. *Cogn Behav Neurol*, 22(4), 205-14 (2009)

223. V. W. Henderson: Action of estrogens in the aging brain: dementia and cognitive aging. *Biochim Biophys Acta*, 1800(10), 1077-83 (2010)

224. F. Blanc, P. Poisbeau, F. Sellal, C. Tranchant, J. de Seze and G. Andre: [Alzheimer disease, memory and estrogen]. *Rev Neurol (Paris)*, 166(4), 377-88 (2010)

225. V. W. Henderson: Estrogens, episodic memory, and Alzheimer's disease: a critical update. *Semin Reprod Med*, 27(3), 283-93 (2009)

226. N. Kandiah and H. H. Feldman: Therapeutic potential of statins in Alzheimer's disease. *J Neurol Sci*, 283(1-2), 230-4 (2009)

227. E. Biondi: Statin-like drugs for the treatment of brain cholesterol loss in Alzheimer's disease. *Curr Drug Saf*, 2(3), 173-6 (2007)

228. B. McGuinness, J. O'Hare, D. Craig, R. Bullock, R. Malouf and P. Passmore: Statins for the treatment of dementia. *Cochrane Database Syst Rev*(8), CD007514 (2010)

229. D. D. Waters: Exploring new indications for statins beyond atherosclerosis: Successes and setbacks. *J Cardiol*, 55(2), 155-62 (2010)

230. H. H. Feldman, R. S. Doody, M. Kivipelto, D. L. Sparks, D. D. Waters, R. W. Jones, E. Schwam, R. Schindler, J. Hey-Hadavi, D. A. DeMicco and A. Breazna: Randomized controlled trial of atorvastatin in mild to moderate Alzheimer disease: LEADe. *Neurology*, 74(12), 956-64 (2010)

231. B. McGuinness and P. Passmore: Can statins prevent or help treat Alzheimer's disease? *J Alzheimers Dis*, 20(3), 925-33 (2010)

232. C. Cramer, M. N. Haan, S. Galea, K. M. Langa and J. D. Kalbfleisch: Use of statins and incidence of dementia and cognitive impairment without dementia in a cohort study. *Neurology*, 71(5), 344-50 (2008)

233. E. Vos and H. H. Nehrlich: Use of statins and incidence of dementia and cognitive impairment without dementia in a cohort study. *Neurology*, 73(5), 406; author reply 406-7 (2009)

234. T. C. Piermartiri, C. P. Figueiredo, D. Rial, F. S. Duarte, S. C. Bezerra, G. Mancini, A. F. de Bem, R. D. Prediger and C. I. Tasca: Atorvastatin prevents hippocampal cell death, neuroinflammation and oxidative stress following amyloid-ß(1-40) administration in mice: evidence for dissociation between cognitive deficits and neuronal damage. *Exp Neurol*, 226(2), 274-84 (2010)

235. D. L. Sparks, R. J. Kryscio, D. J. Connor, M. N. Sabbagh, L. M. Sparks, Y. Lin and C. Liebsack: Cholesterol and cognitive performance in normal controls and the influence of elective statin use after conversion to mild cognitive impairment: results in a clinical trial cohort. *Neurodegener Dis*, 7(1-3), 183-6 (2010)

236. S. P. Glasser, V. Wadley, S. Judd, B. Kana, V. Prince, N. Jenny, B. Kissela, M. Safford, R. Prineas and G. Howard: The association of statin use and statin type and cognitive performance: analysis of the reasons for geographic and racial differences in stroke (REGARDS) study. *Clin Cardiol*, 33(5), 280-8 (2010)

237. L. Galatti, G. Polimeni, F. Salvo, M. Romani, A. Sessa and E. Spina: Short-term memory loss associated with rosuvastatin. *Pharmacotherapy*, 26(8), 1190-2 (2006)

238. D. S. King, A. J. Wilburn, M. R. Wofford, T. K. Harrell, B. J. Lindley and D. W. Jones: Cognitive impairment associated with atorvastatin and simvastatin. *Pharmacotherapy*, 23(12), 1663-7 (2003)

239. L. R. Wagstaff, M. W. Mitton, B. M. Arvik and P. M. Doraiswamy: Statin-associated memory loss: analysis of 60 case reports and review of the literature. *Pharmacotherapy*, 23(7), 871-80 (2003)

240. P. van Vliet, W. van de Water, A. J. de Craen and R. G. Westendorp: The influence of age on the association between cholesterol and cognitive function. *Exp Gerontol*, 44(1-2), 112-22 (2009)

241. J. Savory, C. Exley, W. F. Forbes, Y. Huang, J. G. Joshi, T. Kruck, D. R. McLachlan and I. Wakayama: Can the controversy of the role of aluminum in Alzheimer's disease be resolved? What are the suggested approaches to this controversy and methodological issues to be considered? *J Toxicol Environ Health*, 48(6), 615-35 (1996)

242. P. E. Newman: Could diet be one of the causal factors of Alzheimer's disease? *Med Hypotheses*, 39(2), 123-6 (1992)

243. J. L. Domingo: Aluminum and other metals in Alzheimer's disease: a review of potential therapy with chelating agents. *J Alzheimers Dis*, 10(2-3), 331-41 (2006)

244. M. A. Smith, X. Zhu, M. Tabaton, G. Liu, D. W. McKeel, Jr., M. L. Cohen, X. Wang, S. L. Siedlak, B. E. Dwyer, T. Hayashi, M. Nakamura, A. Nunomura and G. Perry: Increased iron and free radical generation in preclinical Alzheimer disease and mild cognitive impairment. *J Alzheimers Dis*, 19(1), 363-72

245. R. W. Shin, T. P. Kruck, H. Murayama and T. Kitamoto: A novel trivalent cation chelator Feralex dissociates binding of aluminum and iron associated with hyperphosphorylated tau of Alzheimer's disease. *Brain Res*, 961(1), 139-46 (2003)

246. E. House, J. Collingwood, A. Khan, O. Korchazkina, G. Berthon and C. Exley: Aluminium, iron, zinc and copper influence the in vitro formation of amyloid fibrils of Aß42 in a manner which may have consequences for metal chelation therapy in Alzheimer's disease. *J Alzheimers Dis*, 6(3), 291-301 (2004)

247. H. Atamna and W. H. Frey, 2nd: A role for heme in Alzheimer's disease: heme binds amyloid-ß and has altered metabolism. *Proc Natl Acad Sci U S A*, 101(30), 11153-8 (2004)

248. G. K. Gouras and M. F. Beal: Metal chelator decreases Alzheimer ß-amyloid plaques. *Neuron*, 30(3), 641-2 (2001)

249. A. Gnjec, J. A. Fonte, C. Atwood and R. N. Martins: Transition metal chelator therapy--a potential treatment for Alzheimer's disease? *Front Biosci*, 7, d1016-23 (2002)

250. B. Regland, W. Lehmann, I. Abedini, K. Blennow, M. Jonsson, I. Karlsson, M. Sjogren, A. Wallin, M. Xilinas and C. G. Gottfries: Treatment of Alzheimer's disease with clioquinol. *Dement Geriatr Cogn Disord*, 12(6), 408-14 (2001)

251. D. R. Crapper McLachlan, A. J. Dalton, T. P. Kruck, M. Y. Bell, W. L. Smith, W. Kalow and D. F. Andrews: Intramuscular desferrioxamine in patients with Alzheimer's disease. *Lancet*, 337(8753), 1304-8 (1991)

252. T. Priel, B. Aricha-Tamir and I. Sekler: Clioquinol attenuates zinc-dependent ß-cell death and the onset of insulitis and hyperglycemia associated with experimental type I diabetes in mice. *Eur J Pharmacol*, 565(1-3), 232-9 (2007)

253. L. J. Fischer and S. A. Hamburger: Inhibition of alloxan action in isolated pancreatic islets by superoxide dismutase, catalase, and a metal chelator. *Diabetes*, 29(3), 213-6 (1980)

254. P. Cutler: Deferoxamine therapy in high-ferritin diabetes. *Diabetes*, 38(10), 1207-10 (1989)

255. P. Dongiovanni, L. Valenti, A. Ludovica Fracanzani, S. Gatti, G. Cairo and S. Fargion: Iron depletion by deferoxamine up-regulates glucose uptake and insulin signaling in hepatoma cells and in rat liver. *Am J Pathol*, 172(3), 738-47 (2008)

256. R. C. Cooksey, D. Jones, S. Gabrielsen, J. Huang, J. A. Simcox, B. Luo, Y. Soesanto, H. Rienhoff, E. D. Abel and D. A. McClain: Dietary iron restriction or iron chelation protects from diabetes and loss of ß-cell function in the obese (ob/ob lep-/-) mouse. *Am J Physiol Endocrinol Metab*, 298(6), E1236-43 (2010)

257. H. D. Venters, Jr., L. E. Bonilla, T. Jensen, H. P. Garner, E. Z. Bordayo, M. M. Najarian, T. A. Ala, R. P. Mason and W. H. Frey, 2nd: Heme from Alzheimer's brain inhibits muscarinic receptor binding via thiyl radical generation. *Brain Res*, 764(1-2), 93-100 (1997)

258. H. Zheng, L. M. Weiner, O. Bar-Am, S. Epsztejn, Z. I. Cabantchik, A. Warshawsky, M. B. Youdim and M. Fridkin: Design, synthesis, and evaluation of novel bifunctional iron-chelators as potential agents for neuroprotection in Alzheimer's, Parkinson's, and other neurodegenerative diseases. *Bioorg Med Chem*, 13(3), 773-83 (2005)

259. G. Liu, P. Men, G. Perry and M. A. Smith: Chapter 5 - Development of iron chelator-nanoparticle conjugates as potential therapeutic agents for Alzheimer disease. *Prog Brain Res*, 180, 97-108 (2009)

260. J. Y. Lee, J. E. Friedman, I. Angel, A. Kozak and J. Y. Koh: The lipophilic metal chelator DP-109 reduces amyloid pathology in brains of human ß-amyloid precursor protein transgenic mice. *Neurobiol Aging*, 25(10), 1315-21 (2004)

261. G. Liu, M. R. Garrett, P. Men, X. Zhu, G. Perry and M. A. Smith: Nanoparticle and other metal chelation therapeutics in Alzheimer disease. *Biochim Biophys Acta*, 1741(3), 246-52 (2005)

262. G. Liu, P. Men, P. L. Harris, R. K. Rolston, G. Perry and M. A. Smith: Nanoparticle iron chelators: a new therapeutic approach in Alzheimer disease and other neurologic disorders associated with trace metal imbalance. *Neurosci Lett*, 406(3), 189-93 (2006)

263. G. Liu, P. Men, G. Perry and M. A. Smith: Nanoparticle and iron chelators as a potential novel Alzheimer therapy. *Methods Mol Biol*, 610, 123-44 (2010)

264. G. Liu, P. Men, W. Kudo, G. Perry and M. A. Smith: Nanoparticle-chelator conjugates as inhibitors of amyloid-ß aggregation and neurotoxicity: a novel therapeutic approach for Alzheimer disease. *Neurosci Lett*, 455(3), 187-90 (2009)

265. H. Zheng, M. B. Youdim and M. Fridkin: Site-activated multifunctional chelator with acetylcholinesterase and neuroprotective-neurorestorative moieties for Alzheimer's therapy. *J Med Chem*, 52(14), 4095-8 (2009)

266. H. Zheng, M. B. Youdim and M. Fridkin: Site-activated chelators targeting acetylcholinesterase and monoamine oxidase for Alzheimer's therapy. *ACS Chem Biol*, 5(6), 603-10 (2010)

267. W. Huang, D. Lv, H. Yu, R. Sheng, S. C. Kim, P. Wu, K. Luo, J. Li and Y. Hu: Dual-target-directed 1,3-diphenylurea derivatives: BACE 1 inhibitor and metal chelator against Alzheimer's disease. *Bioorg Med Chem*, 18(15), 5610-5 (2010)

268. M. Singh, M. Arseneault, T. Sanderson, V. Murthy and C. Ramassamy: Challenges for research on polyphenols from foods in Alzheimer's disease: bioavailability, metabolism, and cellular and molecular mechanisms. *J Agric Food Chem*, 56(13), 4855-73 (2008)

269. Y. J. Wang, P. Thomas, J. H. Zhong, F. F. Bi, S. Kosaraju, A. Pollard, M. Fenech and X. F. Zhou: Consumption of grape seed extract prevents amyloid-ß deposition and attenuates inflammation in brain of an Alzheimer's disease mouse. *Neurotox Res*, 15(1), 3-14 (2009)

270. K. A. Dasilva, J. E. Shaw and J. McLaurin: Amyloid-ß fibrillogenesis: structural insight and therapeutic intervention. *Exp Neurol*, 223(2), 311-21 (2010)

271. E. M. Janle, M. A. Lila, M. Grannan, L. Wood, A. Higgins, G. G. Yousef, R. B. Rogers, H. Kim, G. S. Jackson, L. Ho and C. M. Weaver: Pharmacokinetics and tissue distribution of 14C-labeled grape polyphenols in the periphery and the central nervous system following oral administration. J Med Food, 13(4), 926-33 (2010)

272. E. Savaskan, G. Olivieri, F. Meier, E. Seifritz, A. Wirz-Justice and F. Muller-Spahn: Red wine ingredient resveratrol protects from ß-amyloid neurotoxicity. Gerontology, 49(6), 380-3 (2003)

273. V. Vingtdeux, U. Dreses-Werringloer, H. Zhao, P. Davies and P. Marambaud: Therapeutic potential of resveratrol in Alzheimer's disease. BMC Neurosci, 9 Suppl 2, S6 (2008)

274. S. S. Karuppagounder, J. T. Pinto, H. Xu, H. L. Chen, M. F. Beal and G. E. Gibson: Dietary supplementation with resveratrol reduces plaque pathology in a transgenic model of Alzheimer's disease. *Neurochem Int*, 54(2), 111-8 (2009)

275. P. Marambaud, H. Zhao and P. Davies: Resveratrol promotes clearance of Alzheimer's disease amyloid-ß peptides. *J Biol Chem*, 280(45), 37377-82 (2005)

276. V. Vingtdeux, L. Giliberto, H. Zhao, P. Chandakkar, Q. Wu, J. E. Simon, E. M. Janle, J. Lobo, M. G. Ferruzzi, P. Davies and P. Marambaud: AMP-activated protein kinase signaling activation by resveratrol modulates amyloid-ß peptide metabolism. *J Biol Chem*, 285(12), 9100-13 (2010)

277. S. Dore: Unique properties of polyphenol stilbenes in the brain: more than direct antioxidant actions; gene/protein regulatory activity. *Neurosignals*, 14(1-2), 61-70 (2005)

278. B. N. Ramesh, T. S. Rao, A. Prakasam, K. Sambamurti and K. S. Rao: Neuronutrition and Alzheimer's disease. *J Alzheimers Dis*, 19(4), 1123-39 (2010)

279. T. S. Anekonda: Resveratrol--a boon for treating Alzheimer's disease? *Brain Res Rev*, 52(2), 316-26 (2006)

280. W. Qin, T. Yang, L. Ho, Z. Zhao, J. Wang, L. Chen, W. Zhao, M. Thiyagarajan, D. MacGrogan, J. T. Rodgers, P. Puigserver, J. Sadoshima, H. Deng, S. Pedrini, S. Gandy, A. A. Sauve and G. M. Pasinetti: Neuronal SIRT1 activation as a novel mechanism underlying the prevention of Alzheimer disease amyloid neuropathology by calorie restriction. *J Biol Chem*, 281(31), 21745-54 (2006)

281. J. Wang, H. Fivecoat, L. Ho, Y. Pan, E. Ling and G. M. Pasinetti: The role of Sirt1: at the crossroad between promotion of longevity and protection against Alzheimer's disease neuropathology. *Biochim Biophys Acta*, 1804(8), 1690-4 (2010)

282. D. Kim, M. D. Nguyen, M. M. Dobbin, A. Fischer, F. Sananbenesi, J. T. Rodgers, I. Delalle, J. A. Baur, G. Sui, S. M. Armour, P. Puigserver, D. A. Sinclair and L. H. Tsai: SIRT1 deacetylase protects against neurodegeneration in models for Alzheimer's disease and amyotrophic lateral sclerosis. *EMBO J*, 26(13), 3169-79 (2007)

283. W. Qin, M. Chachich, M. Lane, G. Roth, M. Bryant, R. de Cabo, M. A. Ottinger, J. Mattison, D. Ingram, S. Gandy and G. M. Pasinetti: Calorie restriction attenuates Alzheimer's disease type brain amyloidosis in Squirrel monkeys (Saimiri sciureus). *J Alzheimers Dis*, 10(4), 417-22 (2006)

284. W. Qin, W. Zhao, L. Ho, J. Wang, K. Walsh, S. Gandy and G. M. Pasinetti: Regulation of forkhead transcription factor FoxO3a contributes to calorie restriction-induced prevention of Alzheimer's disease-type amyloid neuropathology and spatial memory deterioration. *Ann N Y Acad Sci*, 1147, 335-47 (2008)

285. Y. Koyama, K. Abe, Y. Sano, Y. Ishizaki, M. Njelekela, Y. Shoji, Y. Hara and M. Isemura: Effects of green tea on gene expression of hepatic gluconeogenic enzymes in vivo. *Planta Med*, 70(11), 1100-2 (2004)

286. D. F. Obregon, K. Rezai-Zadeh, Y. Bai, N. Sun, H. Hou, J. Ehrhart, J. Zeng, T. Mori, G. W. Arendash, D. Shytle, T. Town and J. Tan: ADAM10 activation is required for green tea (-)-epigallocatechin-3-gallate-induced α-secretase cleavage of amyloid precursor protein. *J Biol Chem*, 281(24), 16419-27 (2006)

287. S. A. Mandel, T. Amit, L. Kalfon, L. Reznichenko, O. Weinreb and M. B. Youdim: Cell signaling pathways and iron chelation in the neurorestorative activity of green tea polyphenols: special reference to epigallocatechin gallate (EGCG). *J Alzheimers Dis*, 15(2), 211-22 (2008)

288. S. A. Mandel, T. Amit, O. Weinreb, L. Reznichenko and M. B. Youdim: Simultaneous manipulation of multiple

brain targets by green tea catechins: a potential neuroprotective strategy for Alzheimer and Parkinson diseases. *CNS Neurosci Ther*, 14(4), 352-65 (2008)

289. A. Smith, B. Giunta, P. C. Bickford, M. Fountain, J. Tan and R. D. Shytle: Nanolipidic particles improve the bioavailability and α-secretase inducing ability of epigallocatechin-3-gallate (EGCG) for the treatment of Alzheimer's disease. *Int J Pharm*, 389(1-2), 207-12 (2010)

290. S. A. Frautschy and G. M. Cole: Why pleiotropic interventions are needed for Alzheimer's disease. *Mol Neurobiol*, 41(2-3), 392-409

291. T. Sobow: Combination treatments in Alzheimer's disease: risks and benefits. *Expert Rev Neurother*, 10(5), 693-702 (2010)

Abbreviations: AD: Alzheimer's disease, ADDL: Amyloid-derived diffusible ligand, ApoE-ε4: Apoliprotein E, ε4 allele, AßPP: Amyloid-ß precursor protein, AßPP-Aß: amyloid-ß fragment of amyloid-ß precursor protein, BACE1: Beta secretase 1, CNS: Central nervous system, COX2: Cyclooxygenase-2, CSF: Cerebrospinal fluid, DIO: Diet induced obesity, EGCG: Epigallocatechin-3-gallate, ER: Endoplasmic reticulum, GLP-1: Glucagon-like peptide-1, GSK-3ß: Glycogen synthase kinase-3ß, HMG-CoA: 3-Hydroxy-3-methyl-glutaryl-CoA, IGF: Insulin-like growth factor, LDL: Low density lipoprotein, MCI: Mild cognitive impairment, MMSE: Mini-mental state examination, MRI: Magnetic resonance imaging, NASH: Non-alcoholic steatohepatitis, NSAID: Non-steroidal anti-inflammatory drug, PET: Positron emission tomography, PI3 kinase: Phosphoinositol-3-kinase, PPAR: Peroxisome proliferator-activated receptor, PS: Presenilin, RNS: Reactive nitrogen species, ROS: Reactive oxygen species, SIRT1: Sirtuin 1 gene or protein, T1DM: Type 1 diabetes mellitus, T2DM: Type 2 diabetes mellitus

Key Words: Amyloid, Anti-oxidants, Brain diabetes, Brain insulin resistance, Incretins, Insulin, Insulin sensitizers, Liver-Brain-Axis, Metal Chelation, Neuroprotection, Nitrosamine, Oxidative Stress, Polyphenols, Statins, Streptozotocin, Tau, Type 3 diabetes

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